

Fig. 1

1 MTSLMLLLLFAFVQPCASIVEKRCGPIDIRNRPWDIKPQWSKLGDPNEKDLAQORMVNCT
 61 VVEGSLTISFVLKHKTKAQEEMHRSLOPRYSQDEFITFPHLREITGTLLVFETEGLVDLR
 121 KIFPNLRVIGGRSLIQHYALIIYRNPDL EIGLDKLSVIRNGGVRIIDNRKLCYTKTIDWK
 181 HLITSSINDVVVDNAAEYAVTETGLMCPRGACEEDKGESKCHYLEEKNQEQQVERVQSCW
 241 SNTTCQKSCAYDRLLPTKEIGPGCDANGDRCHDQCVGGCERVNDATACHACKNVYHKGKC
 301 IEKCD AHL YLLLQRRCVTREQCLQ LNPVLSNKTVP I KATAGLCSDKCPDGYQ INPDDHRE
 361 CRKCVGKCEIVCEINHVIDTFPKAQAIRLCNIIDGNLTIEIRGKQDSGMASELKDIFANI
 421 HTITGYLLVRQSSPFISLNMFRNLRRIEAKSLFRNLYAITVFENPNLKKLFDSTDTLTD
 481 RGTVSIANNKMLCFKYIKQLMSKLNIPLDPIDQSEGTNGEKAICEDMAINVSITAVNADS
 541 VFFSWPSFNITDIDQRFGLGYELFFKEVPRIDENMTIEEDRSACVDSWQSVFKQYYETS
 601 GEPTPDIFMDIGPRERIRPNTLYAYYVATQMV LHAGAKNGVSKIGFVRTSYTTPDPPTLA
 661 LAQVDSDAIHITWEAPLQPNGDLTHYTIMWRENEVSPYEEAEKFCTDASTPANRQRTKDP
 721 KETIVADKPDIPSSRTVAPTLLTMMGHEDQOKTCAATPGCCSCSAIEESSEQNKKKRPD
 781 PMSAIESSAFENKLLDEVLMPRDTRVRRSIEDANRVSEELEKAENLGKAPKTLGGKKPL
 841 IHISKKKPSSSSTTSTPAPTIASMYALTRKPTTVPGTRIRLYEIEPLGSWAINVSALA
 901 LDNSYVIRNLKHYTLIAISLSACQNMTPVGASCSISHRAGALKRTKHITDIDKVLNETIE
 961 WRFMNNSQQVNVTWDPPTTEVNGGIFGYVVKLKSVDGSIVMTRCVGAKRGYSTRNQGVLF
 1021 QNLADGRYFVSVTATS VH GAGPEAESDPIVVMTPGFFTVEIILGMLLVFLILMSIAGCI
 1081 IYIIYIQVRYGKKVKALSDFMQLNPEQCVDNKNYADDWELRQDDVVLGQQCGEGSFQKVYL
 1141 GTGNNVVS LMGDRFGPCA IKIN VDDPASTENLNYLMEANIMKNFKTNFIVQLYGVISTVQ
 1201 PAMVVMEMMDLGNLRDYLRSKREDEVFNEDCNFFDIIPRDKFHEWAAQICDGMAYLES
 1261 KFCHRD LAARNCMINRDETVKIGDFGMARDLFQHDYKPSGKRMPVVRWMSPESLKDQKF
 1321 DSKSDVWSFGVVL YEMVTLGAQPYIGLSNDEV LNYIGMARKVIKKPECCENYWKVMKMC
 1381 WRYSRDRPTFLQLVHLIAAEASPEFRDLSFVLTDNQMILDDSEALDLD DIDDTDMNDQV
 1441 VEVAPDVENVEVQSDSERRNTDSIPLKQFKTIPPINATTSHSTISIDETPMKAKQREGSL
 1501 DEEVALMNHSGGPSDAEVRTYAGDGDVERDVRENDVPTRRNTGASTSSYTGGGPYCLTN
 1561 RGGSNERGAGFGEAVRLTDGVGSGHLNDDDDVEKEISSMDTRRSTGASSSSYGVPTNWS
 1621 GNRGATYYTSKAQQAATAAAAAAALQQQQONGGRGDRLTQLPGTGHLQSTRGGQDGDQIE
 1681 TEPKNYRNNGSPSRNGNSRDIFNGRSAFGENEHLIEDNEHHPLV

Fig. 2A

1	ggtttaatta	cccaagtttg	agctccaaga	gcacacatct	gacgtcggga
51	ttctactgta	ctccccgaaa	aaccaacaaa	aaacacaagt	ttttgaacac
101	ttgtaaatgc	agacagaacg	atgacgagaa	tgaatattgt	cagatgtcgg
151	agacgacaca	aaattttgga	aaatttggaa	gaagagaatc	tcggcccagag
201	ctgctcgtcg	acgacttcaa	caaccgctgc	caccgaagct	ctcggaacaa
251	ccactgagga	tatgaggctt	aagcagcagc	gaagctcgtc	gcgtgccacg
301	gagcacgata	ttgtcgacgg	caatcaccac	gacgacgagc	acatcacaa
351	gagacggctt	cgacttgtca	aaaattcgcg	gacgcggcgt	agaacgacgc
401	ccgattcaag	tatggactgc	tatgaggaaa	acccgccatc	acaaaaactt
451	caataaatta	ttcttggatt	tctaaaaagt	catcaatgac	gtcattaatg
501	cttttactgc	tattcgcttt	tgtacagccg	tgtgcctcaa	tagtcgaaaa
551	acgatgcggc	ccaatcgata	ttcgaaatag	gccgtgggat	attaagccgc
601	aatggtcgaa	acttggat	ccgaacgaaa	aagatttggc	tggtcagaga
651	atggtcaact	gcacagtgg	ggaaggttcg	ctgacaatct	catttgtact
701	gaaacacaag	acaaaagcac	aagaagaaat	gcacgaagt	ctacagccaa
751	gatattccca	agacgaattt	atcacttttc	cgcatctacg	tgaaattact
801	ggaactctgc	tcgtttttga	gactgaagga	ttagtggatt	tgcgtaaaat
851	tttcccaaat	cttcgtgtaa	ttggaggccg	ttcgtgatt	caacactatg
901	cgctgataat	ttatcgaaat	ccggatttgg	agatcggctc	tgacaagctt
951	tccgtaattc	gaaatggtgg	tgtacggata	atcgataatc	gaaaactgtg
1001	ctacacgaaa	acgattgatt	ggaaacattt	gatcacttct	tccatcaacg
1051	atggtgtcgt	tgataatgct	gccgagtacg	ctgtcactga	gactggattg
1101	atgtgcccac	gtggagcttg	cgaagaggat	aaaggcgaat	caaagtgtca
1151	ttatttggag	gaaaagaatc	aggaacaagg	tgtcgaaaga	gttcagagtt
1201	gttggtcgaa	caccacttgc	caaaagtctt	gtgcttatga	tcgtcttctt
1251	ccaacgaaag	aaatcggacc	gggatgtgat	gcgaacggcg	atcgatgtca
1301	cgatcaatgc	gtgggcggtt	gtgagcgtgt	gaatgatgcc	acagcatgcc
1351	acgcgtgcaa	gaatgtctat	cacaagggaa	agtgtatcga	aaagtgtgat
1401	gctcacctgt	accttctcct	tcaacgtcgt	tgtgtgaccc	gtgagcagtg
1451	tctgcagctg	aatccggtgc	tctcgaacaa	aacagtgcct	atcaaggcga
1501	cggcaggcct	ttgctcggat	aaatgtcccg	atggttatca	aatcaaccgg
1551	gatgatcatc	gagaatgccg	aaaatgcgtt	ggcaagtgtg	agattgtgtg
1601	cgagatcaat	cacgtcattg	atacgtttcc	gaaggcacag	gcgatcaggc
1651	tatgcaatat	tattgacgga	aatctgacga	tcgagattcg	cggaaaacag
1701	gattcgggaa	tggcgtccga	gttgaaggat	atatttgcca	acattcacac
1751	gatcaccggc	tacctgttgg	tacgtcaatc	gtcaccgttt	atctcgttga
1801	acatgttccg	gaatttacga	cgtattgagg	caaagtcact	gttcagaaat
1851	ctatatgcta	tcacagtttt	tgaaaatccg	aatttaaaaa	agctattcga
1901	ttcaacgacg	gatttgacgc	ttgatcgtgg	aactgtgtca	attgccaaata
1951	acaagatggt	atgcttcaag	tatatcaagc	agctaattgtc	aaagttaaata
2001	ataccactcg	atccgataga	tcaatcagaa	gggacaaatg	gtgagaagg
2051	aatctgtgag	gatatggcaa	tcaacgtgag	catcacagcg	gtcaacgcgg
2101	actcggctct	ctttagttgg	ccctcattca	acattaccga	tatagatcag
2151	cgaaagtttc	tcggctacga	gctcttcttc	aaagaagtcc	cacgaatcga
2201	tgagaacatg	acgatcgaag	aggatcgaag	tgctgtgtgc	gattcgtggc
2251	agagtgtctt	caaacagtac	tacgagacgt	cgaacggtga	accgaccccg
2301	gacattttta	tggatattgg	accgcgcgag	cgaattcggc	cgaatacgtc
2351	ctacgcgtac	tatgtggcga	cgcagatggt	gttgcatgcc	ggtgcgaaga
2401	acggtgtatc	gaagattggt	tttgtgagga	cgagctacta	tacgcctgat
2451	cctccgacgt	tggcactagc	gcaagtcgat	tcggacgcta	ttcatattac
2501	gtgggaagcg	ccgctccaac	cgaacggaga	cctcacgcac	tacacaatta
2551	tgtggcgtga	gaatgaagtg	agcccgtacg	aggaagccga	aaagttttgt
2601	acagatgcaa	gcacccccgc	aaatcgacaa	cgcacgaaag	atccgaaaga
2651	gacgattgta	gccgataagc	cagtcgatat	tccgtcatca	cgtaccgtag
2701	ctccgacact	tttgactatg	atgggtcacg	aagatcagca	gaaaacgtgc

Fig. 2B (sheet 1 of 3)

2751	gctgcaacgc	ccggttggtg	ttcgtggtcg	gctatcgaag	aatcatcgga
2801	acagaacaag	aagaagcgac	cggatccgat	gtcggcgatc	gaatcatctg
2851	catttgagaa	taagctggtg	gatgagggtt	taatgccgag	agacacgatg
2901	cgagtgaagc	gatcaattga	agacgcgaat	cgagtcagtg	aagagttgga
2951	aaaagctgaa	aatttgggaa	aagctccaaa	aactctcggt	ggaaagaagc
3001	cgctgatcca	tatttcgaag	aagaagccgt	cgagcagcag	caccacatcc
3051	acaccggctc	caacgatcgc	atcaatgtat	gccttaacaa	ggaaaccgac
3101	tacgggtgccg	ggaacaagga	ttcggctcta	cgagatctac	gaacctttac
3151	ccggaagctg	ggcgattaat	gtatcagctc	tggcattgga	taatagttat
3201	gtgatacgaa	atttgaagca	ttacacactt	tatgcgattt	ctctatccgc
3251	gtgccaaaac	atgacagtac	ccggagcatc	ttgctcaata	tcccatcggt
3301	cgggagcatt	gaaacgaaca	aaacacatca	cagacattga	taaagtgttg
3351	aatgaaacaa	ttgaatggag	atztatgaat	aatagtcaac	aagtcaacgt
3401	gacgtgggat	ccaccgactg	aagtgaatgg	tggaaatattc	ggttatgttg
3451	taaagcttaa	gtcaaaagtc	gatggatcaa	ttgttatgac	gagatgtgtc
3501	ggtgcgaaga	gaggatattc	aacacggaat	cagggtgtcc	tattccagaa
3551	tttggccgat	ggacgttatt	ttgtctcagt	aacggcgacc	tctgtacacg
3601	gcgctggacc	ggaagccgaa	tcctccgacc	caatcgctcg	catgacgcca
3651	ggcttcttca	ctgtggaaat	cattctcggc	atgcttctcg	tctttttgat
3701	tttaatgtca	attgccggtt	gtataatcta	ctactacatt	caagtacgct
3751	acggcaaaaa	agtgaagct	ctatctgact	ttatgcaatt	gaatcccga
3801	tattgtgtgg	acaataagta	caatgcagac	gattgggagc	tacggcagga
3851	tgatgttgtg	ctcggacaac	agtgtggaga	gggatcattc	ggaaaaggtg
3901	acctaggaac	tggaaataat	gttgtttctc	tgatgggtga	tcgtttcgga
3951	ccgtgtgcta	ttaagattaa	tgtagatgat	ccagcgctcg	ctgagaatct
4001	caactatctc	atggaagcta	atattatgaa	gaactttaag	actaacttta
4051	tcgtccaaact	gtacggagtt	atctctactg	tacaaccagc	gatggttgtg
4101	atggaaatga	tggatcttgg	aaatctccgt	gactatctcc	gatcgaaaacg
4151	cgaagacgaa	gtgttcaatg	agacggactg	caactttttc	gacataatcc
4201	cgagggataa	attccatgag	tgggccgcac	agatttgtga	tggatatggcg
4251	tacctggagt	cgctcaagtt	ttgccatcga	gatctcgccg	cacgtaattg
4301	catgataaat	cgggatgaga	ctgtcaagat	tggagatttc	ggaatggctc
4351	gtgatctatt	ctatcatgac	tattataaag	catcgggcaa	gcgtatgatg
4401	cctgttcgat	ggatgtcacc	cgagtcggtg	aaagacggaa	agtttgactc
4451	gaaatctgat	gttttgagct	tcggagttgt	tctctatgaa	atggttacac
4501	tcggtgctca	gccatatatt	ggtttgagta	atgatgaggt	gttgaattat
4551	attggaatgg	cccggaaagt	tatcaagaag	cccgaatgtt	gtgaaaacta
4601	ttggtataag	gtgatgaaaa	tgtgctggag	atactcacct	cgggatcgct
4651	cgacgttcct	ccagctcggt	catcttctag	cagctgaagc	ttcaccagaa
4701	ttccgagatt	tatcatttgt	cctaaccgat	aatcaaata	tccttgacga
4751	ttcagaagca	ctggatcttg	atgatattga	tgatactgat	atgaatgatc
4801	aggttgtcga	ggtggcaccg	gatgttgaga	acgtcgaggt	tcagagtgat
4851	tcggaacgct	ggaatacggg	ttcaataaccg	ttgaaacagt	ttaagacgat
4901	ccctccgatc	aatgcgacga	cgagtcattc	gacaatatcg	attgatgaga
4951	caccgatgaa	agcgaagcag	cgagaaggat	cgctggatga	ggagtacgca
5001	ttgatgaatc	atagtggagg	tcggagtgat	gcggaagttc	ggacgtatgc
5051	tggatgatga	gattatgtgg	agagagatgt	tcgagagaat	gatgtgccaa
5101	cgcgacgaaa	tactggtgca	tcaacatcaa	gttacacagg	tgggtgtcca
5151	tattgcctaa	caaactcgtg	tggttcaaat	gaacgaggag	ccggtttcgg
5201	tgaagcagta	cgattaaactg	atgggtgttg	aagtggacat	ttaaatagatg
5251	atgattatgt	tgaaaaagag	atatcatcca	tggatacgcg	ccggagcacg
5301	ggcgccctga	gctcttccta	cggtgttcca	cagacgaatt	ggagtggaaa
5351	tcgtgggtgcc	acgtattata	cgagtaaagc	tcaacaggca	gcaactgcag
5401	cagcagcagc	agcagcagct	ctccaacagc	aacaaaatgg	tggtcgaggc
5451	gatcgattaa	ctcaactacc	cggaactgga	catttacaat	cgacacgtgg
5501	tggacaagat	ggagattata	ttgaaactga	accgaaaaat	tatagaaata

Fig. 2B (sheet 2 of 3)

5551	atggatctcc	atcgcgaaac	ggcaacagcc	gtgacatddd	caacggacgt
5601	tcggctttcg	gtgaaaatga	gcatctaata	gaggataatg	agcatcatcc
5651	acttgtctga	aacccccaaa	aaatcccgcc	tcttaaatta	tacattatct
5701	cccacattat	catatctcta	cacgaataat	ggattdtdtd	tcagattdtd
5751	tctgaaaaat	tctgaataat	tttaccat	ttttcaaata	tcgtattdtd
5801	tttttggtat	tacccc			

Fig. 2B (sheet 3 of 3)

T05250-5699560

IGF-IR RGAIRIEKNADLCYLSLSTWDDSLTDAVSNNYIVGKPPK..EGG.DLCPGTMEKPKCEKTTNNENYNR.....CMTTNRCKKMC.....PSTC
 InR RGVRIEKNNEKCYLATIDWSRITDSDVEDNYIVLNKDDNE.EGG.DICPGTAGKTNCPTAVINGQFVER.....CMTSHCKORVC.....PTIC
 DinR RGVRIEKNHKKCYDRITDIDWLELJAENESQVLTGTEKEKESLSKCPGEIRIEEGHDNTALEGELNASCOLHNNRRLCWNHSLCOTKC.....PEKC
 DAF-2 NCGVRIIDNRKLCYTKTIDWKHLITSSINDVVVDNAEYAVTETGLMCPRGACEEDKESKCHYLEKNQEQGVVERVQSCWNSNTTCORS CAYDRLLLETKE

IGF-IR GKRACTENNECCHPECLGSC.SAPDNDTACVACHHYHYAGVCPVAPCPPNTYRFEGRWCVDVDRDFCANL...SAESSDSEGFVIHDEGECMOECPSGKIRN
 InR KSHGCTAEGLCCHSECLGNC.SOPDDPKCVACRNFLDRCVETCPPPYVHEQDWRCVNFSECDLHHKCKNSRRQCHQYVIHNNKCIPECPSCGYTMN
 DinR .RNNCIDEHTCCSQDCGGGVIDKNGESGISCRNVSFNNICMDSCEPKGYQE.DSRGVTANECITUTKFETNSVYSG...IPYNGQCITHCPTGY.QK
 DAF-2 IGPGCDANGDRCHDQCVGGC.ERVNDATACHACKNVVHKCKIEKCDHAHLVLELQRRCVTREQCLOQNPVLSNKTVP...IKATAGLCSDKCEDGYQIN
 Y (mg43) YS (aa187)

IGF-IR GSQSMYCIPCEGPCPKVCEEEKTKTIDSVTSQOMLOGCTIPKGN..MLNIR..GNNIASELENFMGLTEVATGVVKIRHSHALVSLSEKKNLRLTLG
 InR SSN.LLCTPCLGPPKPVCHLLEGEKTTIDSVTSQOELRGCTVNGS..LITNIRG..GNNLAAELEANLGLLEEISGYIKIRERSYALVSLSEKKNLRLTLG
 DinR SENKRMCEPCPG..KCDKECSSLIDSLERAREFHGCTVITGTEPTTISHKRESGAHVMDLKYGLAAVHKHQSMMVHLTYGKSLKEFQSLTEISG
 DAF-2 PDDHRECRKGVKCEIVCEI...NHVIDAFPKAQAIRLCNITIDGN..ETELIEGKQDSGMASELKIDIFANHTHTTGYLLVQSSP%ISLNMERNLRRLEA

IGF-IR VSFYVLDNQLQQMDWDHNRNLTIKAKGMVFAFPKLCVSELYRNEZVTGTGR.QSKGDINTRNNGERASCESDVVHFTSTTTTSKN.....
 InR ETLEIGN.VSFYALDNONLRQMDWSKHNLTTITQKLFHYNPKLCVSELYRNEZVTGTGR.QERNDIALKTNGDQASCENELKFSYIRTSFD.....
 DinR DPPMDADKVALVVDNRDLDELNG.PNQTVEFRKGGVFEHFNPKLCVSTINQLLPNLASPKPFPEKSDGADSNRGCCTAVINVTLSQVGOANSALN
 DAF-2 KSLFR.NLVAITVRENPNPKKLED.STTDLTLDRTGTVSIANNKMLCFKYLKQLMSKLINIP...LDPIDQSEGTNGEKAICEDMAINVSITAVNADS.....
 L (e1368)T (e1365) N (sa229)

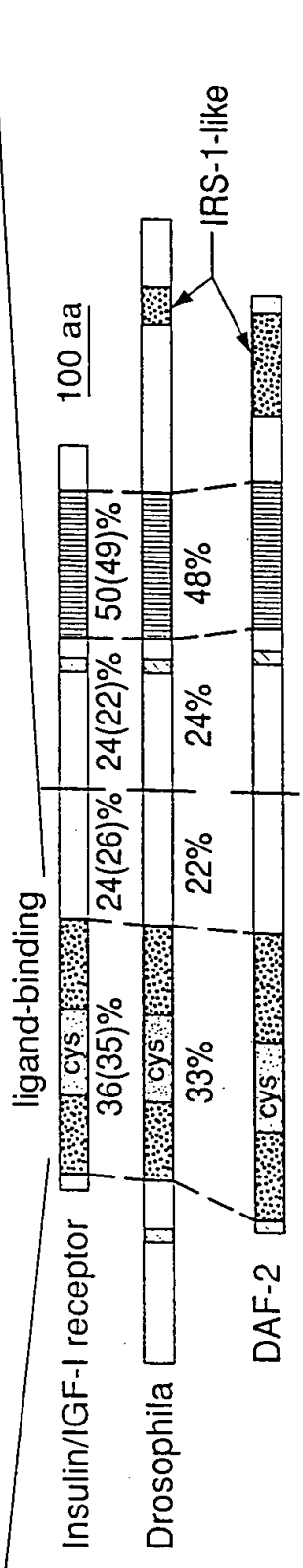


Fig. 2C (sheet 1 of 2)

FO5260-26929660

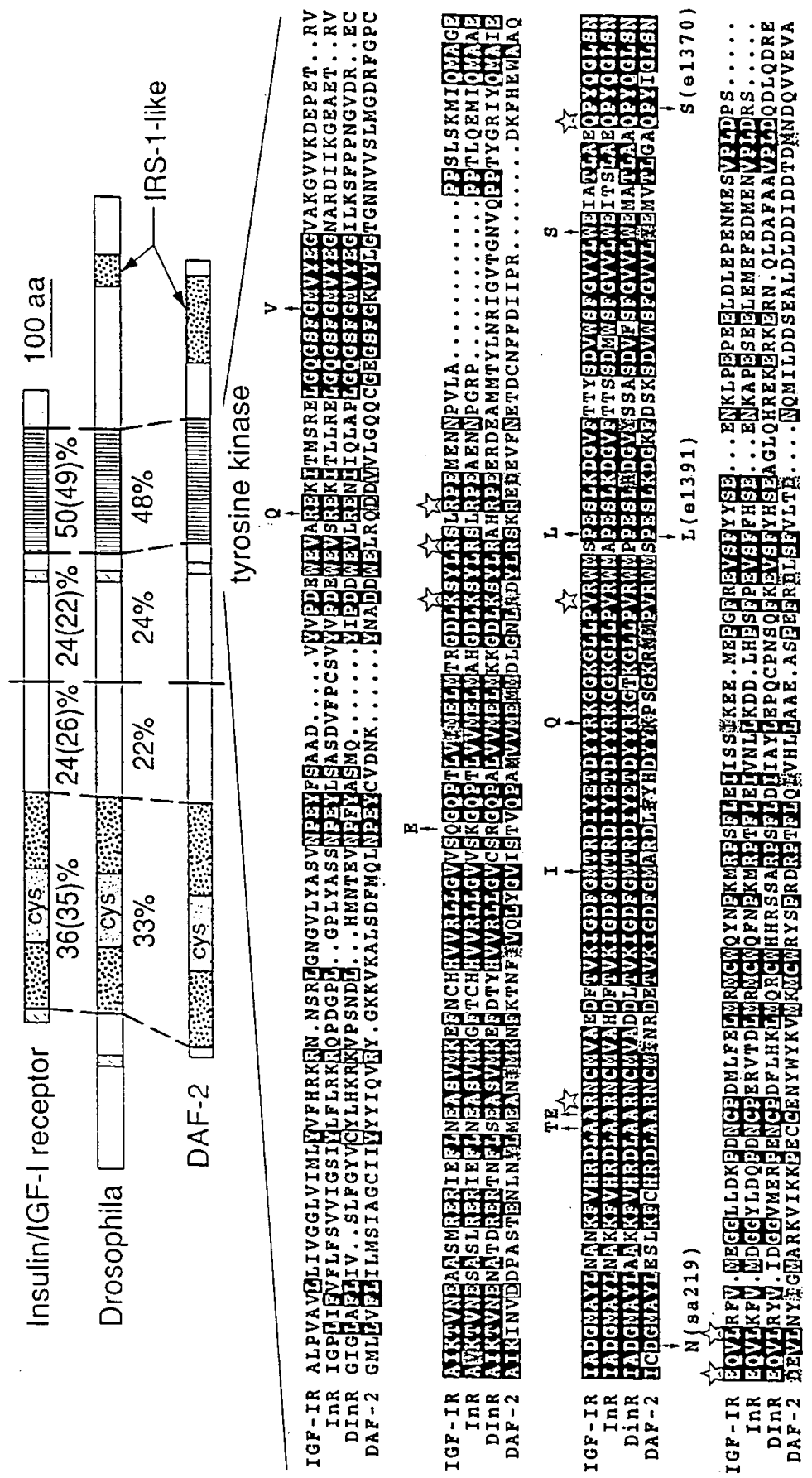


Fig. 2C (sheet 2 of 2)

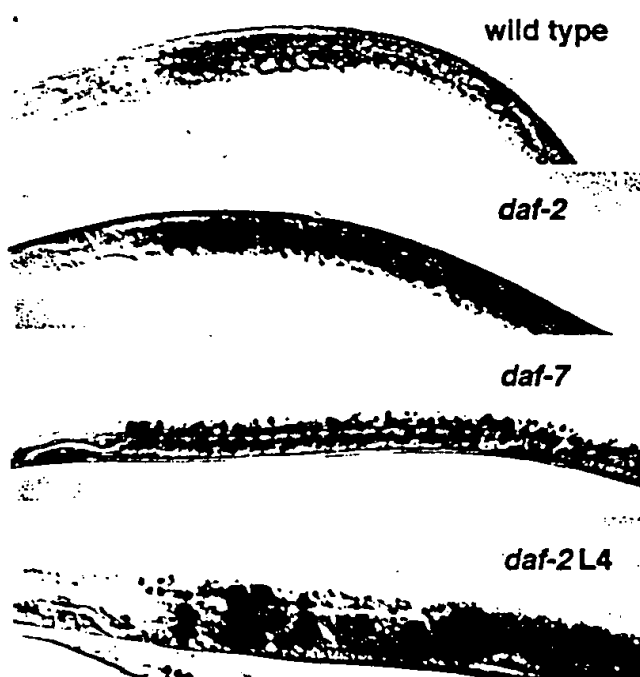


Fig. 3

095260* 26929660

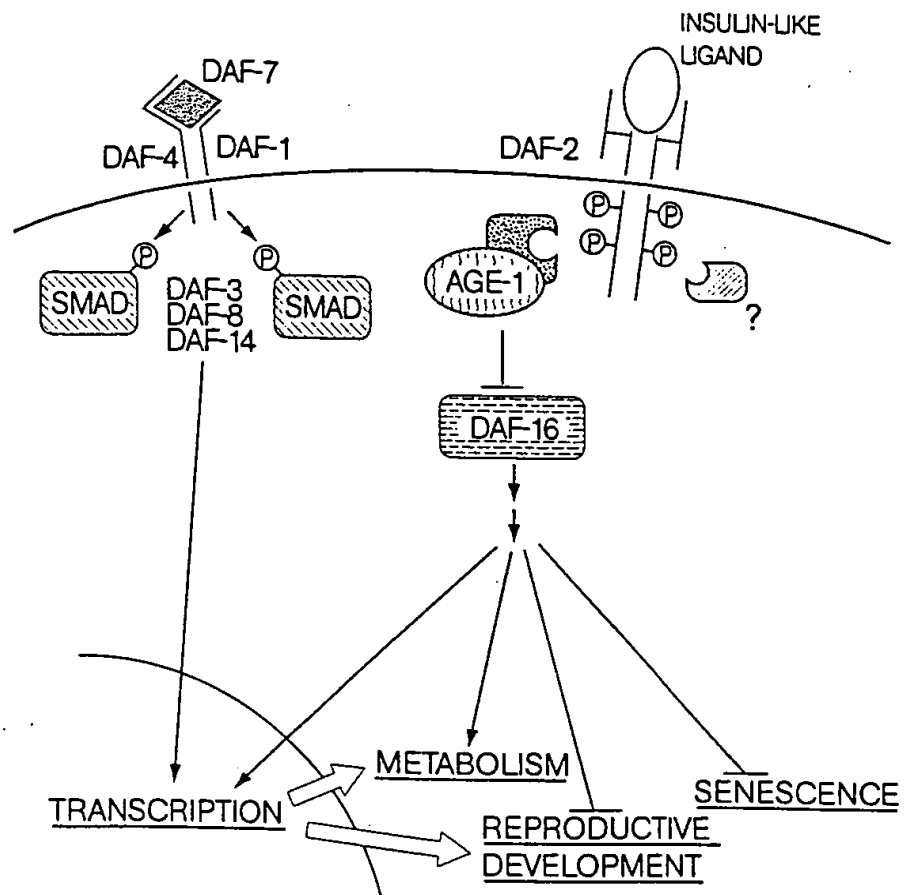


Fig. 4

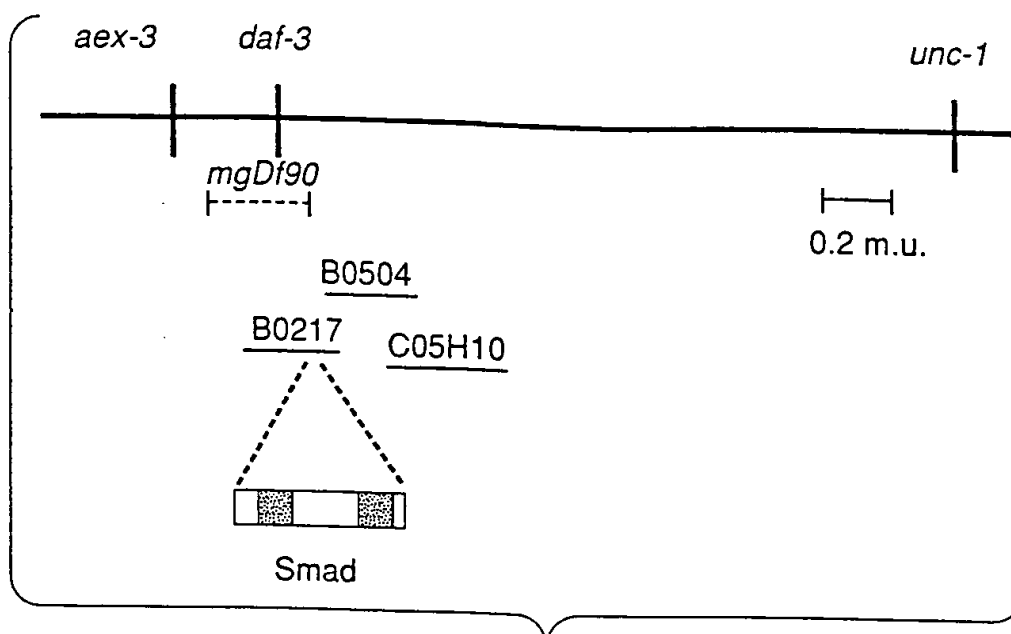


Fig. 5A

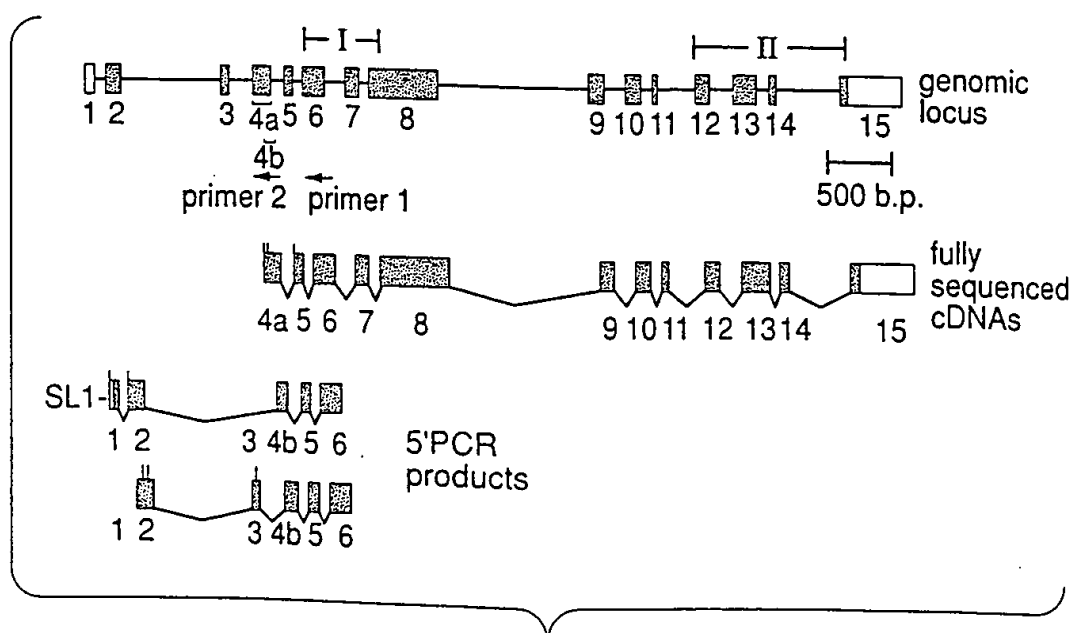


Fig. 5B

```

DAF-3 .NIDREFDQKACESLVKKLKDKKNDLQNLIDVVLSSKGTKYTGCTIPRTLDTG
      | | | | | | | | | | | | | | | | | | | | | | | | | | | |
DPC4  GGESETFAKRAIESLVKKLKEKKDELDSLITAITNGAHPKSCVTIQRTLDTG
      mg125 P->L
      RLQVHGRKGFPFHVYGYGLWRFNEMTKNETRHVDHCKHAFEMKSDMVCVNPYH
      | | | | | | | | | | | | | | | | | | | | | | | | | | | |
      RLQVAGRKGFPFHVYARLWRWPD LHKNELKHVKYCQYAFDLKCD SVCVNPYH

```

DAF-3 IVYYEKNLQIGE..KKCSRGNFHVDGGFI..CSENRYSLGLEPNPIREPVAFKV
| | | | | | | | | | | | | | |
DPC4 IAYFEMDVQVGGETFKVPSSCPIVTVDGYVDPSSGDRFCGLQLSNVHRTEAIERA
mg132 G->E
RKAIVDGIRFSYKKDGSVWLQNRMKYPVFVTSGYLDEQSGGLKKDKVHKVYGCA
| | | | | | | | | | | | | | |
RLHIGKGVQLECKGEGDVWVRCLSDHAVFVQSYYLDREAGRAPGDAVHKIYPSA

SIKTGFNVSQOIIRDALLSKQMA....TMYLQGKLTPMNYIYEKKTQEELRRE
| | | | | | | | | | | | | | |
YIKVFDLRQCHRQMQQQAATAQAAAAAQAAAVAGNIPGPSVGGIAPAISLSAA

ATRTTDSLAKYCCVRVSFCKGFGEAYPERPSIHDCPVWIELKINIA YDFMD
| | | | | | | | | | | | | | |
AGIGVDDLRLRCILRMSFVKGWGPDPYP.RQSIKETPCWIEIHLHRA LQLLD

Fig. 5C

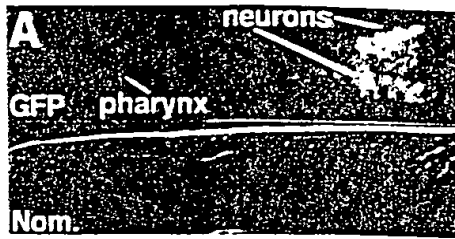


Fig. 6A

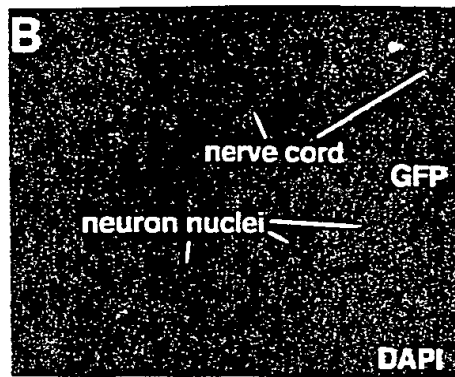


Fig. 6B

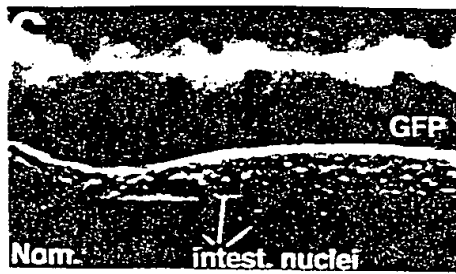


Fig. 6C

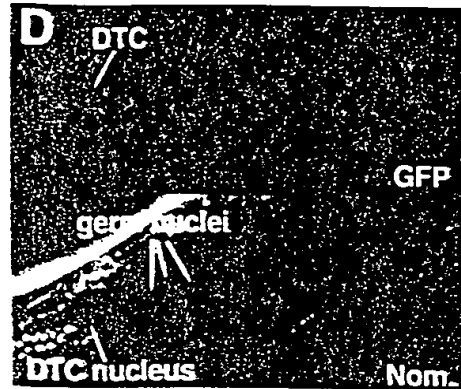


Fig. 6D

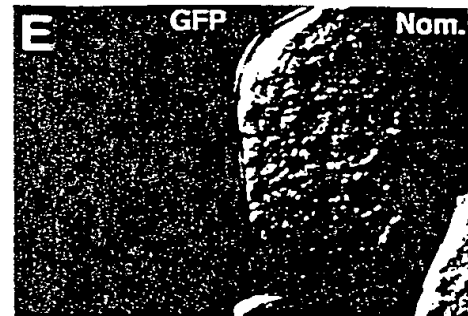


Fig. 6E



Fig. 6F



Fig. 6G

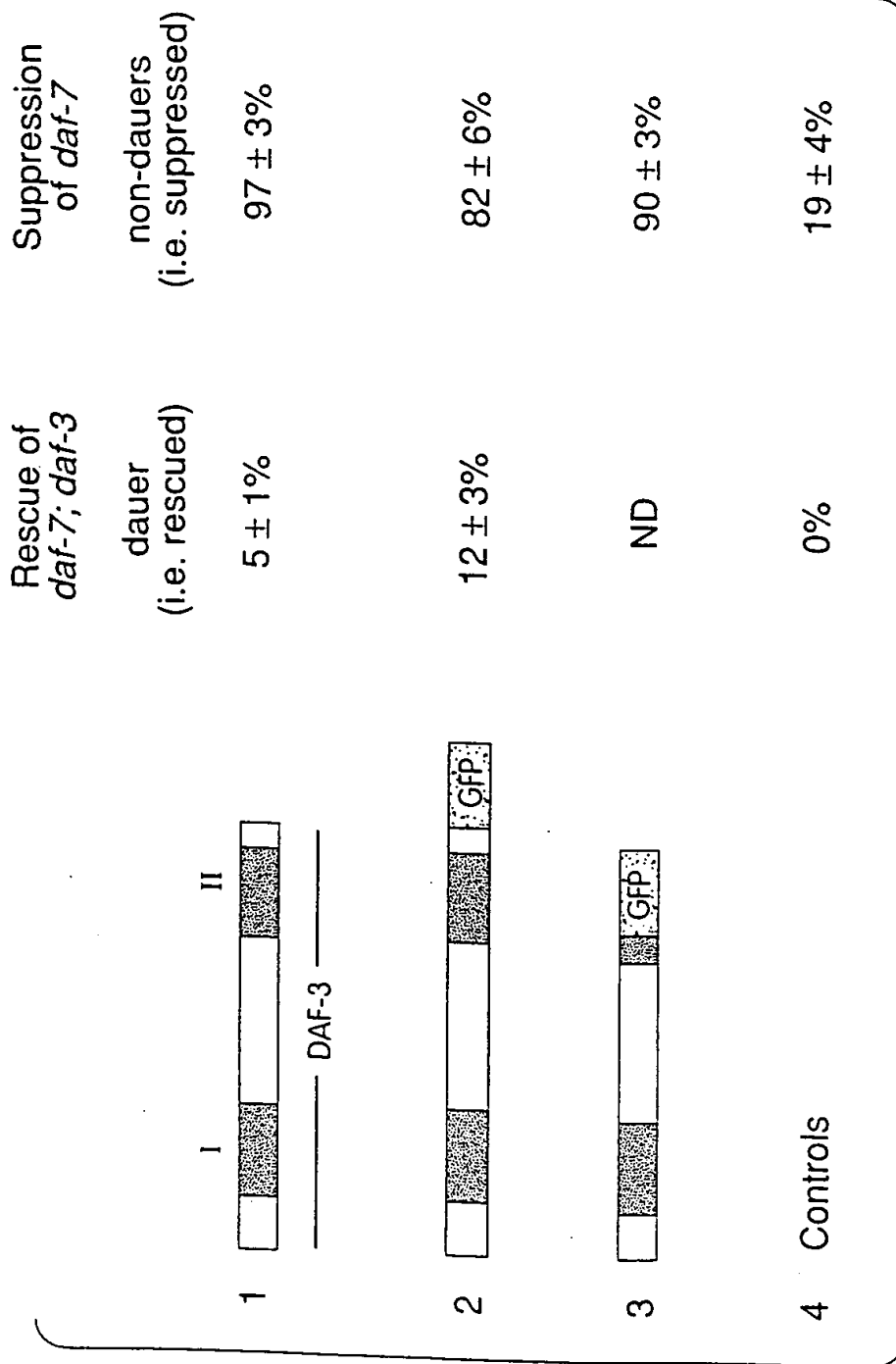


Fig. 7

0963603-09204
FOI260-20929660

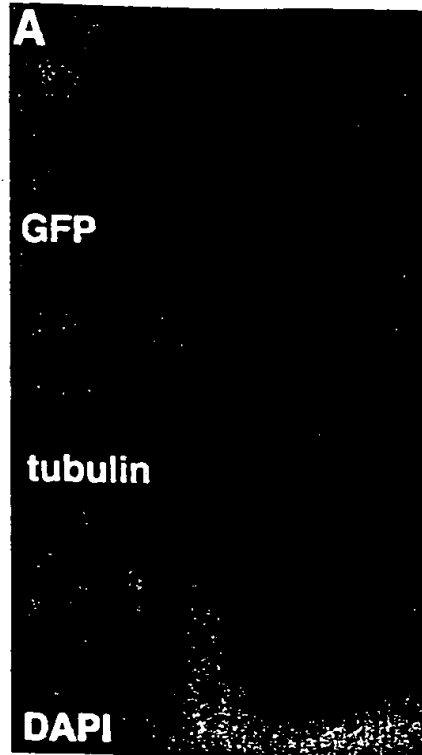


Fig. 8A

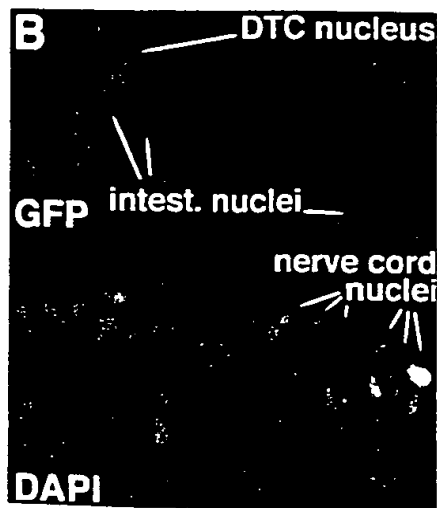


Fig. 8B

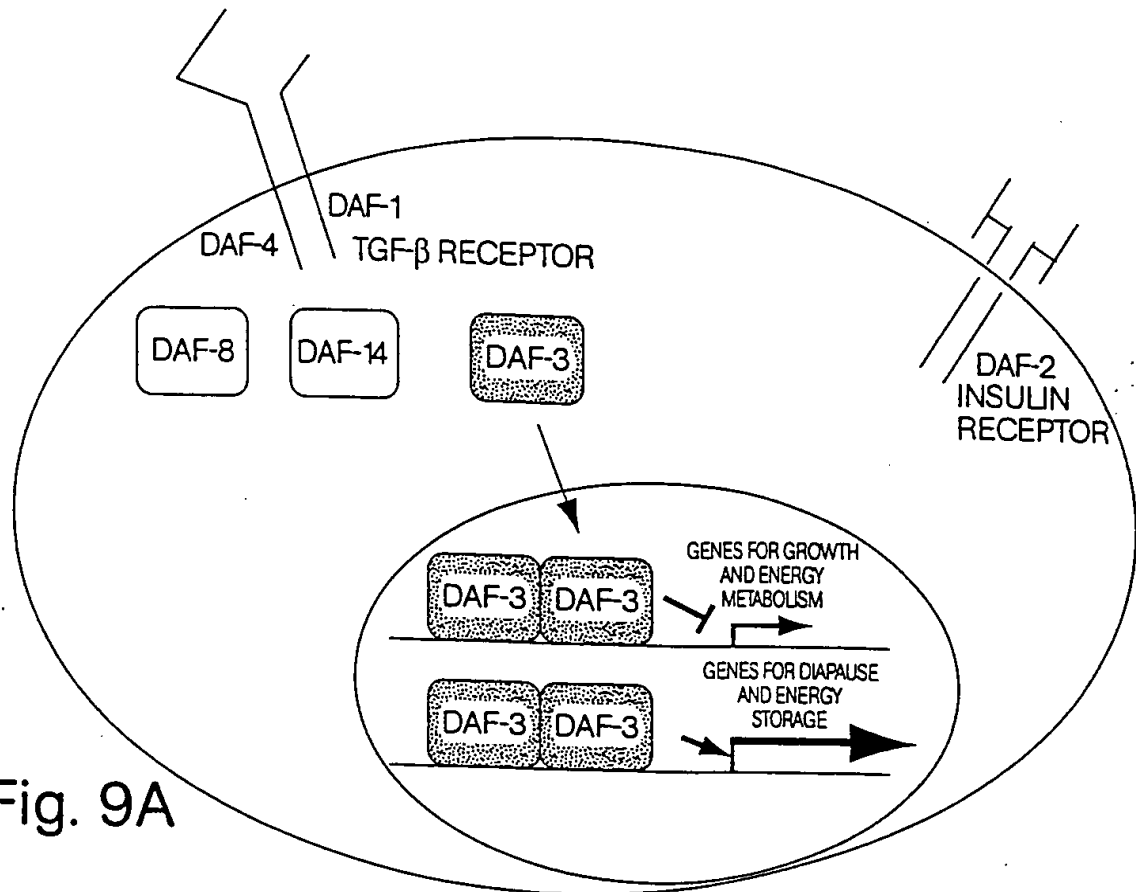


Fig. 9A

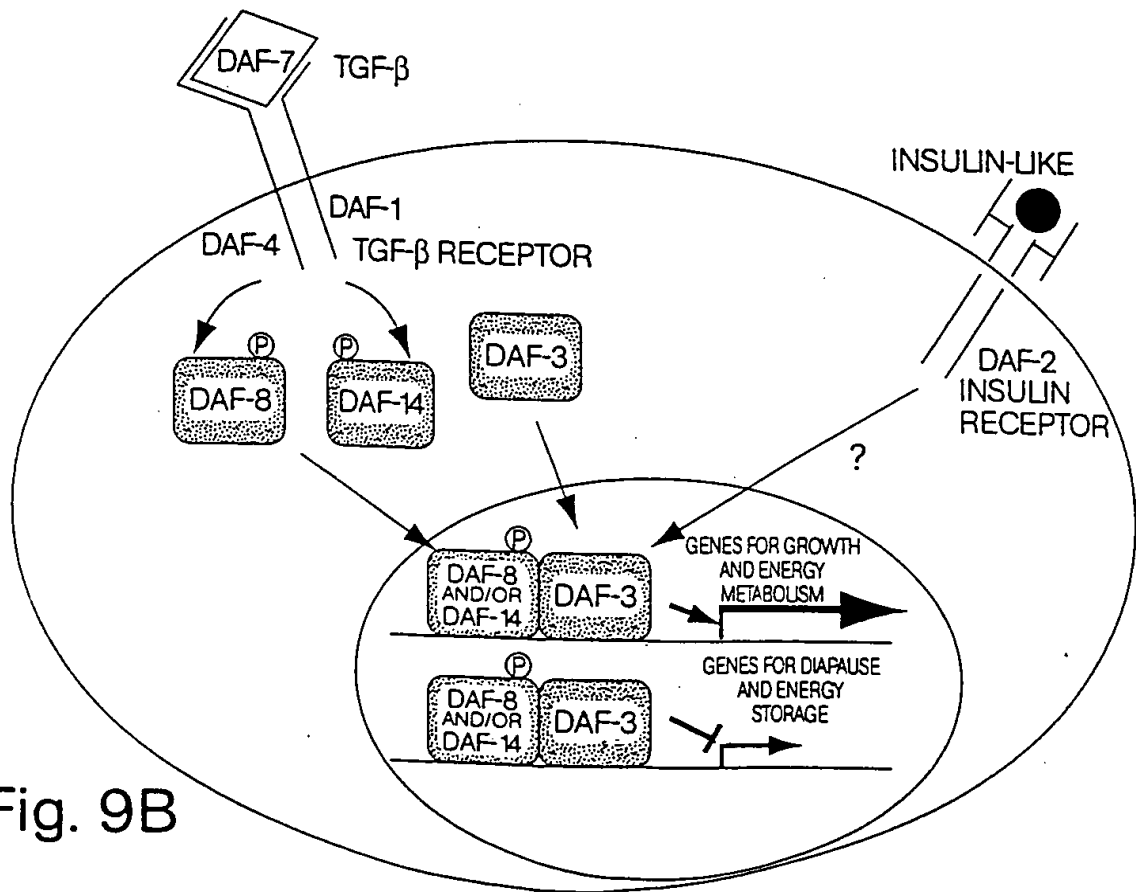


Fig. 9B

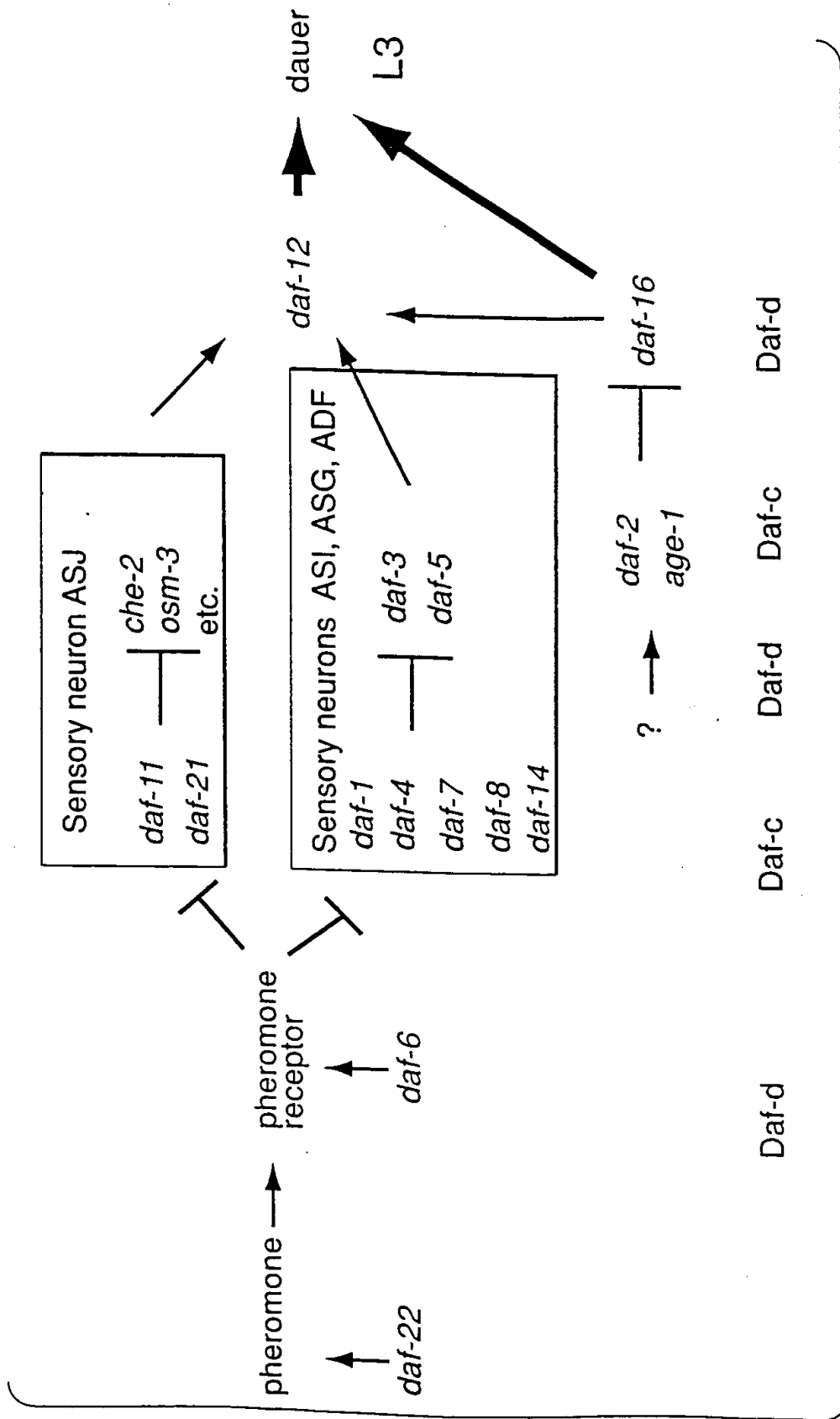


Fig. 10

1 atgaagctaa tagcaacttc tcttctagtt cccgacgagc acacaccgat
 51 gatgtcacca gtgaatacaa ctacaaagat tctacaacgg agtggtatta
 101 aatggaaat cccgccatat ttggatccag acagtcagga tgatgacccg
 151 gaagatggtg tcaactaccc ggatccagat ttatttgaca caaaaaacac
 201 aatatgacc gagtacgatt tggatgtgtt gaagcttgga aaaccagcag
 251 tagatgaagc acggaaaaag atcgaagttc cgcacgctag tgcgccgcca
 301 aacaaaattg tagaatattt gatgtattat agaacgttaa aagaaagtga
 351 actcatacaa ctgaatgcgt atcggacaaa acgaaatcga ttatcgttga
 401 acttggtcaa aaacaatatt gatcgagagt tgcacaaaaa agcttgcgag
 451 tccctggtga aaaaattgaa ggataagaag aatgatctcc agaacctgat
 501 tgatgtggtt ctttcaaaag gtacaaaata taccggttgc attacaattc
 551 caaggacact tgatggccgg ttacaggtcc acggaagaaa aggtttccct
 601 cacgtagtct atggcaaact gtggagggtt aatgaaatga caaaaaacga
 651 aacgcgtcat gtggaccact gcaagcacgc atttgaaatg aaaagtgaca
 701 tggatatgct gaatccctat cactacgaaa ttgtcattgg aactatgatt
 751 gttgggcaga gggatcatga caatcgagat atgccgccgc cacatcaacg
 801 ctaccacact ccaggtcggc aggatccagt tgacgatatg agtagattta
 851 taccaccagc ttccattcgt ccgcctccga tgaacatgca cacaaggcct
 901 cagcctatgc ctcaacaatt gccttcagtt ggcgcaacgt ttgcccattc
 951 tctcccacat caggcgccac ataaccagg ggtttcacat ccgtactcca
 1001 ttgctccaca gaccattac ccgttgaaca tgaacccaat tccgcaaatg
 1051 ccgcaaatgc cacaaatgcc accacctctc catcagggat atggaatgaa
 1101 tgggcccagat tgctcttcag aaaacaacaa tccattccac caaatcacc
 1151 attataatga tattagccat ccaaatcact attcctacga ctgtggtccg
 1201 aacttgtagc ggtttccaac tccttatccg gattttcacc atcctttcaa
 1251 tcagcaacca caccagccgc cacaactatc acaaaaccat acgtcccaac
 1301 aaggcagtca tcaaccaggg caccaaggtc aggtaccgaa tgatccacca
 1351 atttcaagac cagtgttaca accatcaaca gtcaccttgg acgtgttccg
 1401 tcggtactgt agacagacat ttggaaatcg attttttgaa ggagaaagtg
 1451 aacaatccgg cgcaataatt cggctctagta acaaattcat tgaagaattt
 1501 gattcgccga tttgtggtgt gacagttgtt cgaccgcgga tgacagacgg
 1551 tgagggtttg gagaacatca tgccggaaga tgcaccatat catgacattt
 1601 gcaagttcat tttgaggctc acatcagaaa gtgtaacttt ctcaggagag
 1651 gggccagaag ttagtgattt gaacgaaaaa tggggaacaa ttgtgtacta
 1701 tgagaaaaat ttgcaaattg gcgagaaaaa atgttcgaga ggaaatttcc
 1751 acgtggatgg cggattcatt tgctctgaga atcgttacag tctcggactt
 1801 gagccaaatc caattagaga accagtggcg tttaaagttc gtaaagcaat
 1851 agtggatgga attcgctttt cctacaaaaa agacgggagt gtttggcttc
 1901 aaaaccgcat gaagtacccg gtattttgtc cttctgggta tctcgacgag
 1951 caatcaggag gcctaaagaa ggataaagtg cacaaagttt acggatgtgc
 2001 gtctatcaaa acgtttggct tcaacgtttc caaacaatc atcagagacg
 2051 cgcttctttc caagcaaattg gcaacaatgt acttgcaagg aaaattgact

Fig. 11A (sheet 1 of 2)

2101 ccgatgaatt atatctacga gaagaagact caggaagagc tgcgaaggga
 2151 agcaacacgc accactgatt cattggccaa gtactgttgt gtccgtgtct
 2201 cgttctgcaa aggatttgga gaagcatacc cagaacgccc gtcaattcat
 2251 gattgtccag tttggattga gttgaaaatc aacattgcct acgatttcat
 2301 ggattcaatc tgccagtaca taaccaactg cttcgagccg ctaggaatgg
 2351 aagattttgc aaaattggga atcaacgtca gtgatgacta aatgataact
 2401 tttttcactc accctactag atactgattt agtcttattc caaatcatcc
 2451 aacgatatca aactttttcc tttgaacttt gcatactatg ttatcacaag
 2501 ttccaagcag tttcaataca aacataggat atgttaacaa cttttgataa
 2551 gaatcaagtt accaactgtt cattgtgagc tttgagctgt atagaaggac
 2601 aatgtatccc atacctcaat ctttaatatg catcagtcac tgggtcccgca
 2651 ccaatttttt cgattcgcat atgtcatata ttgcaccgtg gcccttttta
 2701 ttgtaacttt taatatattt tcttcccaac ttgtgaatat gattgatgaa
 2751 ccaccatttt gagtaataaa tgtatttttt gtgg

Fig. 11A (sheet 2 of 2)

0993693-092504

1 gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
 51 ggtgatcatc ataatttaac gggccttccc ggtacctcca tcccgccaca
 101 gttcaactat ttcagccccg gtaccagcac cggaggccccg ctttatggtg
 151 gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201 aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251 tatggctaata gttcccgacg agcacacacc gatgatgtca ccagtgaata
 301 caactacaaa gattctacaa cggagtggta ttaaaatgga aatcccgcca
 351 tatttggatc cagacagtca ggatgatgac ccggaagatg gtgtcaacta
 401 cccggatcca gatttatattg acacaaaaaa cacaaatatg accgagtacg
 451 atttggtatg gttgaagctt ggaaaaccag cagtagatga agcacggaaa
 501 aagatcgaag ttcccgacgc tagtgcgccg ccaaacaaaa ttgtagaata
 551 tttgatgtat tatagaacgt taaaagaaag tgaactcata caactgaatg
 601 cgtatcggac aaaacgaaat cgattatcgt tgaacttggc caaaaacaat
 651 attgatcgag agttcgacca aaaagccttg gagtccctgg tgaaaaaatt
 701 gaaggataag aagaatgatc tccagaacct gattgatgtg gttctttcaa
 751 aaggtaaaaa atataccggt tgcattacaa ttccaaggac acttgatggc
 801 cggttacagg tccacggaag aaaaggtttc cctcacgtag tctatggcaa
 851 actgtggagg tttaatgaaa tgacaaaaaa cgaaacgcgt catgtggacc
 901 actgcaagca cgcatttgaa atgaaaagtg acatgggtatg cgtgaatccc
 951 tatcactacg aaattgtcat tggaaactatg attgttgggc agagggatca
 1001 tgacaatcga gatatgccgc cgccacatca acgctaccac actccaggtc
 1051 ggcaggatcc agttgacgat atgagtagat ttataccacc agcttccatt
 1101 cgtccgcctc cgatgaacat gcacacaagg cctcagccta tgcctcaaca
 1151 attgccttca gttggcgcaa cgtttgcccc tctctccca catcaggcgc
 1201 cacataaacc aggggtttca catccgtact ccattgctcc acagacccat
 1251 taccggttga acatgaacc aattccgcaa atgccgcaa tgccacaaat
 1301 gccaccacct ctccatcagg gatatggaat gaatgggccc agttgctctt
 1351 cagaaaacaa caatccattc caccaaaatc accattataa tgatattagc
 1401 catccaaatc actattccta cgactgtggt ccgaacttgt acgggtttcc
 1451 aactccttat ccggattttc accatccttt caatcagcaa ccacaccagc
 1501 cgccacaact atcacaaaac catacgtccc aacaaggcag tcatcaacca
 1551 gggcaccaag gtcaggatcc gaatgatcca ccaatttcaa gaccagtgtt
 1601 acaaccatca acagtcacct tggacgtgtt ccgtcggtag tgtagacaga
 1651 catttggaat tcgatttttt gaaggagaaa gtgaacaatc cggcgcaata
 1701 attcggctca gtaacaaatt cattgaagaa tttgattcgc cgatttgtgg
 1751 tgtgacagtt gttcgaccgc ggatgacaga cggtagaggt ttggagaaca
 1801 tcatgccgga agatgcacca tatcatgaca tttgcaagtt cattttgagg
 1851 ctcacatcag aaagtgtaac tttctcagga gaggggccag aagttagtga
 1901 tttgaacgaa aaatggggaa caattgtgta ctatgagaaa aatttgcaaa
 1951 ttggcgagaa aaaatgttcg agaggaaatt tccacgtgga tggcggattc
 2001 atttgctctg agaatcgta cagtctcgga cttgagccaa atccaattag
 2051 agaaccagtg gcgtttaaag ttcgtaaagg aatagtggat ggaattcgct

Fig. 11B (sheet 1 of 2)

2101 tttcctacaa aaaagacggg agtgtttggc ttcaaaaccg catgaagtac
 2151 ccggtatttg tcacttctgg gtatctcgac gagcaatcag gaggcctaaa
 2201 gaaggataaa gtgcacaaag ttctacggatg tgcgtctatc aaaacgtttg
 2251 gcttcaacgt ttccaaacaa atcatcagag acgcgcttct ttccaagcaa
 2301 atggcaacaa tgtacttgca aggaaaattg actccgatga attatatcta
 2351 cgagaagaag actcaggaag agctgcgaag ggaagcaaca cgcaccactg
 2401 attcattggc caagtactgt tgtgtccgtg tctcgttctg caaaggattt
 2451 ggagaagcat acccagaacg cccgtcaatt catgattgtc cagtttggat
 2501 tgagttgaaa atcaacattg cctacgattt catggattca atctgccagt
 2551 acataaccaa ctgcttcgag ccgctaggaa tggaagattt tgcaaaattg
 2601 ggaatcaacg tcagtgatga ctaaatagata acttttttca ctcaccctac
 2651 tagatactga tttagtctta ttccaaatca tccaacgata tcaaactttt
 2701 tcctttgaac tttgcatact atgttatcac aagttccaag cagtttcaat
 2751 acaaacatag gatatgttaa caacttttga taagaatcaa gttaccaact
 2801 gttcattgtg agctttgagc tgtatagaag gacaatgtat cccataacctc
 2851 aatctttaat agtcatcagt cactgggtccc gcaccaattt tttcgattcg
 2901 catatgtcat atattgcacc gtggcccttt ttattgtaac ttttaataata
 2951 ttttcttccc aacttgtgaa tatgattgat gaaccaccat tttgagtaat
 3001 aaatgtattt tttgtgg

Fig. 11B (sheet 2 of 2)

F05250-2699660

1	gtaatcaa	at	tgtaaagg	aaatatta	at	agtcagag	ta	cacataaa	atg
51	ggtgatca	tc	ataattta	ac	gggccttc	ccc	ggtacctc	ca	tcccgccaca
101	gttcaact	at	tctcagccc	g	gtaccagca	c	cggaggccc	g	ctttatggtg
151	gaaaacct	tc	tcatggatt	g	gaagatat	tc	ctgatgtaga		ggaatatgag
201	aggaacct	gc	tcggggctg	g	agcaggttt	t	aatctgctca		atgtaggaaa
251	tatggcta	at	gaatttta	aa	caataatca	c	attggacacg		aaaccacctc
301	gtgatgcc	aa	caagtcatt	g	gcattcaat	g	gcgggttgaa		gctaatact
351	ccgaaaact	g	aagttccc	ga	cgagcacaca		ccgatgatgt		caccagtga
401	tacaacta	ca	aagattct	ac	aacggagt	gg	tattaaaatg		gaaatcccgc
451	catatttg	ga	tccagacag	t	caggatgat	g	acccggaaga		tggtgtcaac
501	tacccggat	c	cagatttt	att	tgacacaaaa		aacacaaa	ata	tgaccgagta
551	cgatttgga	t	gtgttgaa	gc	ttggaaaacc		agcagtagat		gaagcacgga
601	aaaagatc	ga	agttccc	gac	gctagtgcgc		cgccaaacaa		aattgtagaa
651	tatttgat	gt	attataga	ac	gttaaaagaa		agtgaactca		tacaactgaa
701	tgcgtatc	gg	acaaaacg	aa	atcgattatc		gttgaacttg		gtcaaaaaca
751	atattgat	c	agagttcg	ac	caaaaagctt		gcgagtcct		ggtgaaaaaa
801	ttgaagg	ata	agaagaat	ga	tctccagaac		ctgattgatg		tggttctttc
851	aaaaggta	ca	aaatatacc	g	gttgcat	ta	aattccaagg		acacttgatg
901	gccggtt	aca	ggtccacg	ga	agaaaagg	tt	tccctcacgt		agtctatggc
951	aaactgtg	ga	ggtttaat	ga	aatgacaaa		aacgaaacgc		gtcatgtgga
1001	ccactgca	ag	cacgcatt	tg	aatgaaaag		tgacatggta		tgcgtagaatc
1051	cctatcact	a	cgaaattg	tc	attggaacta		tgattggttg		gcagagggat
1101	catgaca	atc	gagatatg	cc	gccgccacat		caacgctacc		acactccagg
1151	tcggcagg	at	ccagttgac	g	atatgagtag		atztatacca		ccagcttcca
1201	ttcgtccg	cc	tccgatga	ac	atgcacacaa		ggcctcagcc		tatgcctcaa
1251	caattgc	ctt	cagttggc	gc	aacgtttg	cc	catcctctcc		cacatcaggc
1301	gccacata	ac	ccaggggt	tt	cacatccgta		ctccattgct		ccacagaccc
1351	attaccg	gtt	gaacatga	ac	ccaattccgc		aaatgccgca		aatgccacaa
1401	atgccacc	ac	ctctccat	ca	gggatatgga		atgaatgggc		cgagttgctc
1451	ttcagaaa	ac	aacaatcc	at	tccaccaaaa		tcaccattat		aatgatatta
1501	gccatccaa	aa	tcactatt	cc	tacgactgtg		gtccgaactt		gtacgggttt
1551	ccaactc	ctt	atccggatt	tt	tcaccatcct		ttcaatcagc		aaccacacca
1601	gccgccaca	aa	ctatcacaa	a	accatacgtc		ccaacaaggc		agtcatcaac
1651	cagggcac	ca	aggtcagg	ta	ccgaatgatc		caccaatttc		aagaccagt
1701	ttacaacc	at	caacagtc	ac	cttggacgtg		ttccgtcgg		actgtagaca
1751	gacatttg	ga	aatcgatt	tt	ttgaaggaga		aagtgaacaa		tccggcgcaa
1801	taattcg	gtc	tagtaacaa	a	ttcattgaag		aatttgattc		gccgatttgt
1851	ggtgtgac	ag	ttgttcgac	c	gcggatgaca		gacggtgagg		ttttggagaa
1901	catcatg	ccg	gaagatgc	ac	catatcatga		catttgcaag		ttcattttga
1951	ggctcac	atc	agaaagt	gta	actttctcag		gagagggg	cc	agaagttagt
2001	gatttga	acg	aaaaatg	ggg	aacaattgtg		tactatgaga		aaaatttgca
2051	aattggc	gag	aaaaatg	tt	cgagaggaaa		tttccacgtg		gatggcggat

Fig. 11C (sheet 1 of 2)

2101	tcatttgctc	tgagaatcgt	tacagtctcg	gacttgagcc	aatccaatt
2151	agagaaccag	tggcgtttaa	agttcgtaaa	gcaatagtgg	atggaattcg
2201	cttttcctac	aaaaaagacg	ggagtgtttg	gcttcaaaac	cgcatagaat
2251	acccggtatt	tgtcacttct	gggtatctcg	acgagcaatc	aggaggccta
2301	aagaaggata	aagtgcacaa	agtttacgga	tgtgctgcta	tcaaaacggt
2351	tggcttcaac	gtttccaaac	aatcatcag	agacgcgctt	ctttccaagc
2401	aatggcaac	aatgtacttg	caaggaaaat	tgactccgat	gaattatata
2451	tacgagaaga	agactcagga	agagctgcga	agggaagcaa	cacgcaccac
2501	tgattcattg	gccaagtact	gttgtgtccg	tgtctcgttc	tgcaaaggat
2551	ttggagaagc	ataccagaa	cgcccgtaaa	ttcatgattg	tccagtttgg
2601	attgagttga	aatcaacat	tgcctacgat	ttcatggatt	caatctgcc
2651	gtacataacc	aactgcttcg	agccgctagg	aatggaagat	tttgcaaaat
2701	tgggaatcaa	cgtcagtgat	gactaaatga	taactttttt	cactcaccct
2751	actagatact	gatttagtct	tattccaaat	catccaacga	tatcaaactt
2801	tttcctttga	actttgcata	ctatgttatc	acaagttcca	agcagtttca
2851	atacaaacat	aggatatgtt	aacaactttt	gataagaatc	aagttaccaa
2901	ctgttcattg	tgagctttga	gctgtataga	aggacaatgt	atcccatacc
2951	tcaatcttta	atagtcatca	gtcactggtc	ccgcaccaat	tttttcgatt
3001	cgcataatgc	atatattgca	ccgtggccct	ttttattgta	acttttaata
3051	tattttcttc	ccaacttggt	aatatgattg	atgaaccacc	attttgagta
3101	ataaatgtat	tttttgtgg			

Fig. 11C (sheet 2 of 2)

09963693.092501

1 MKLIATSLLV PDEHTPMMSP VNTTTKILQR SGIKMEIPPY LDPDSQDDDP
 51 EDGVNYPDPD LFDTKNTNMT EYDLVDLKLK KPAVDEARKK IEVPDASAPP
 101 NKIVEYLMYY RTLKESELIQ LNAYRTKRN LSLNLVKNNI DREFDQKACE
 151 SLVKKLKDKK NDQLNLIDVV LSKGTTYTGC ITIPRTLDGR LQVHGRKGFP
 201 HVVYGKLWRF NEMTKNETRH VDHCKHAFEM KSDMVCVNPY HYEIVIGTMI
 251 VGQRDHDNRD MPPPHQRYHT PGRQDPVDDM SRFIPPASIR PPPMNMHTRP
 301 QPMPQQLPSV GATFAHPLPH QAPHNPGVSH PYSIAPQTHY PLNMNPIPQM
 351 PQMPQMPPPL HQGYGMNGPS CSSENNNPFH QNHHYNDISH PNHYSYDCGP
 401 NLYGFPTYP DFHHPFNQQP HQPPQLSQNH TSQQGSHQPG HQGQVPNDPP
 451 ISRPVLQPST VTLDVFRRYC RQTFGNRFFE GESEQSGAII RSSNKFIEEF
 501 DSPICGVTVV RPRMTDGEVL ENIMPEDAPY HDICKFILRL TSESVTFSGE
 551 GPEVSDLNEK WGTIVYYEKN LQIGEKKCSR GNFHVDGGFI CSENRYSLGL
 601 EPNPIREPVA FKVRKAIVDG IRFSYKKDGS VWLQNRMKYP VFVTSGYLDE
 651 QSGGLKKDKV HKVYGCASIK TFGFNVSKQI IRDALLSKQM ATMYLQGLT
 701 PMNYIYEKKT QEELRREATR TTDSLAKYCC VRVSFCKGFG EAYPERPSIH
 751 DCPVWIELKI NIAYDFMDSI CQYITNCFEP LGMEDFAKLG INVSDD

Fig. 12A

1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NVPDEHTPMM SPVNTTTKIL QRSNIKMEIP
 101 PYLDPDSQDD DPEDGVNYPD PDLFDTKNTN MTEYDLVDLK LGKPAVDEAR
 151 KKIEVPDASA PPNKIVEYLM YYRTLKESEL IQLNAYRTKR NRLSLNLVKN
 201 NIDREFDQKA CESLVKKLKD KKNDLQNLID VVLSKGTKYT GCITIPRTLD
 251 GRLQVHGRKG FPHVVGKLW RFNEMTKNET RHVDHCKHAF EMKSDMVCVN
 301 PYHYEIVIGT MIVGQRDHDN RDMPPPHQRY HTPGRQDPVD DMSRFIPPAS
 351 IRPPPMNMHT RPQPMPPQLP SVGATFAHPL PHQAPHNPGV SHPYSIAPQT
 401 HYPLNMNPIP QMPQMPQMP PLHQGYGMNG PSCSSENNNP FHQNHYYNDI
 451 SHPNHYSYDC GPNLYGFPTP YPDFHHPFNQ QPHQPPQLSQ NHTSQQGS HQ
 501 PGHQGQVPND PPISRPVLQP STVTLDVFRY YCRQTFGNRF FEGESEQSGA
 551 IIRSSNKFIE EFDSPICGVT VVRPRMTDGE VLENIMPEDA PYHDICKFIL
 601 RLTSESVTFS GEGPEVSDLN EKWGTIVYYE KNLQIGEKKC SRGNFHV DGG
 651 FICSENRYSL GLEPNPIREP VAFKVRKAIV DGIRFSYKKD GSVWLQNRMK
 701 YPVFVTSGYL DEQSGGLKGD KVHKVYGCAS IKTFGFNVSK QIIRDALLSK
 751 QMATMYLQK LTPMNYIYEK KTQEELRREA TRTTDSLAKY CCVRVSFCKG
 801 FGEAYPERPS IHDCPVWIEL KINIAYDFMD SICQYITNCF EPLGMEDFAK
 851 LGINVSD

Fig. 12B

T05250-2692960

1 MGDHNLTLGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NEFKPIITLD TKPPRDANKS LAFNGGLKLI
 101 TPKTEVPDEH TPMMSPVNTT TKILQRSIGK MEIPPYLDPD SQDDDPEDGV
 151 NYPDPDLFDT KNTNMTEYDL DVLKLGKPAV DEARKKIEVP DASAPPNKIV
 201 EYLMYYRTLK ESELIQLNAY RTRNRRLSLN LVKNNIDREF DQKACESLVK
 251 KLKDKKNDLQ NLIDVVLKSG TKYTGCTITP RTLDGRLQVH GRKGFPFHVY
 301 GKLWRFNEMT KNETRHVDHC KHAFEMKSDM VCVNPHYHYEI VIGTMIVGQR
 351 DHDNRDMPPP HQRYHTPGRQ DPVDDMSRFI PPASIRPPPM NMHTRPQPMP
 401 QQLPSVGATF AHPLPHQAPH NPGVSHPYSI APQTHYPLNM NPQPMPQMP
 451 QMPPPLHQGY GMNGPSCSSE NNNPFHQNH YNDISHPNHY SYDCGPNLYG
 501 FPTPYPDFHH PFNQPHQPP QLSQNHSTQQ GSHQPGHQGQ VPNDPPISRP
 551 VLQPSTVTLD VFRRYCRQTF GNRFFEGESE QSGAIRSSN KFIEEFDSPI
 601 CGVTVVRPRM TDGEVLENIM PEDAPYHDIC KFILRLTSES VTFSGEGPEV
 651 SDLNEKWGTI VYIEKNLQIG EKKCSRGNFH VDGGFICSEN RYSLGLEPNP
 701 IREPVAFKVR KAIVDGIRFS YKKDGSVWLQ NRMKYPVFTV SGYLDEQSGG
 751 LKKDKVHKVY GCASIKTFGF NVSKQIIRDA LLSKQMATMY LQKLTMPNY
 801 IYEKKTQEEL RREATRTDS LAKYCCVRVS FCKGFGEAYP ERPSIHDCPV
 851 WIELKINIAY DFMDISICQYI TNCFEPLGME DFAKLGINVS DD

Fig. 12C

09963693.099601

Fig. 13A

ttacacgtggccaatgcaacaatacatctatcaggaatcgtcagcaaccattccccatcaccattttaaatcaacacaaca
 atccgtatcatccaatgcatcctcatcatcaattacctcatatgcaacaacttctcaacctctattgaatcttaacatg
 acgacgttaacatcttctggcagttccgtggccagttccattggaggcggagctcaatgctctccgtgccgctcgggctc
 ctgaccgctgcaacaaattcctctcaacagcagcagaccgttggtcaaagtcttgctgcatcgggtgccttggtcttcat
 ctggcatgacacttggaatgtcacttaatctgtcacaaggcgggtggtccaatgccggcaaaaaagaagcgttgctgtaag
 aagccaaccgatcaattggcacagaagaaaccgaatccatggggtgaggaatcctattcggatatcattgccaagcatt
 ggaatcggcgccagacggaaggcttaactcaatgagatttatcaatgggtctctgataatattccctactttggagaac
 gatctagtcccgaggaggccgccggatggaagaactcgatccgtcacaatctgtctcttcattctcgtttcatgcgaatt
 cagaatgaaggagccggaagagctcgtgggtggttattaatccagatgcaaagccaggaatgaatccacggcgtacacg
 tgaacgatccaatactattgagacgactacaaaggctcaactcgaaaaatctcgccgaggagccaagaagaggataaagg
 agagagcattgatgggctcccttcaactcgacacttaatggaaattcgattgccggatcgattcaaacgattttctcacgat
 ttgtatgatgatgattcaatgcaaggagcatttgataacgttccatcatcttccgtccccgaactcaatcgaaacctctc
 gattcctggatcgtcgtctcgtgtttctccagctattggaagtgatctatgatgatctagaattcccacatcatgggtg
 gcgaatcgggtccagcaattccaagtgatattggtgatagaactgatcaaatgcgtatcgatgcaactactcatattggt
 ggagttcagattaagcaggagtcgaagccgattaagacggaaccaattgctccaccaccatcataccacgagttgaacag
 tgtccgtggatcgtgtgctcagaatccacttcttcgaaatccaattgtgccaagcactaacttcaagccaatgccactac
 cgggtgcctatggaaactatcaaaatgggtggaataactccaatcaattggctatcaacatccaactcatctccactgcct
 ggaattcaatcgtgtggaattgtagctgcacagcatactgtcgcttcttcacggctcttccaattgatttggaatct
 gacattcccgatcagccactgatggatactatggatggtgatgcattgatcagacatgagctgagtcagctggagggc
 agcatattcattttgatttgtaattctcttcattttgtttccctgggtgtgttcgaaagagagatagcaaagcagcga
 ggagtgagaaatcttccgtcttcacatcttttcaaactccctacacacactcaacgatcatcacagccagaccatcaat
 attcttccaaattttgacgtcgtaatttttttccagtttttcaaaaactctattttctattttctgtcgtttgttccc
 ctttctctcgtctaattccaacacattcatcccagtgacgtcgtgtaataataataaaaatccctcttctctcttctt
 cccctaattgcgaaatatcgaaaaaccgttgattattacctcttttttctgttttttttctctctctctctcccgta
 tccaggttcttcaactctttaaatgctacctctatcccacatcttttctgctgtaaatgttttcgcaatcaaaactgctaaa
 acacattccccaatctgtcttttttaattgaatttttcaaaaaatttgatttcttgatttctcttgtaattctttaattt
 tccctttttttttccccctggtagcaaatgtctagcgattctctttcttttttgtttaactttcacatctggccgattc
 gaatcctccgtatacacacacacatagtaattctacctccaaaattttactgaaagatgtgatccccctctctgtctccctc
 taaaaacattatttgtctgtttgtgtatattgccaccacgtcgatttttaattaaaaccatcggtttttcttctttct
 acttttttctcgaaaaatttaacaacacacaaaaaatccttcaaaaaatctcagtttttaaatgggtgtggcaatatatcg
 gatccccctctacaccagaacagcttgcatttcagagaatgattttcagatttttcatatcacaggcccccttttttt
 gcttggttttttctctacctctcttttttcttctattttctctctctgttttctctctgttatcctgtacattttcc
 ttccaattctttctggctattttctgattttcgagttcatattctctacgtctcactttctctcgcgccacgccccctttt
 tcgtctccctccgcccccaatatattgcgactgtatgatgatgatgatttaataaaaaat

Fig. 13B

MMEMLVDQGTDASSSASTSTSSVSRFGADTFMNTTPDDVMMNDDMEPIPRDR
 CNTWPMRRPQLEPPLNSSPIIHEQIPEEDADLYGSNEQCQQLGGASSNGST
 AMLHTPDGNSHQTSTFPSDFRMSSEPDSTVSGKKTTRRNAWGNMSYAELI
 TTAIMASPEKRLTLAQVYEWVQNVYFRDKGDSNSSAGWKNSIRHNLSLH
 SRFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSR
 RGAKKRIKERMALMGSLHSTLNGNSIAGSIQTISHDLYDDDSMQGAFDNVPS
 SFRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDR
 TDQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPPLR
 RNPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVA
 AQHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL

Fig. 14A

MQQYIYQESSATIPHHHLNQHNPNPYHPMHPHHQLPHMQQLPQPLNLNMTT
 LTSSGSSVASSIGGGAQCSPCASGSSTAATNSSQQQQQTVGQMLAASVPCSS
 SGMTLGMSLNLSQGGGMPAKKKRCKKPTDQLAQKKPNPWGEESYSDIIA
 KALESAPDGRKLNEIYQWFSDNIPYFGERSSP~~E~~EAAAGWKNSIRHNLSLHS
 RFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSR
 GAKKRIKERMALMGSLHSTLNGNSIAGSIQTISHDLYDDDSMQGAFDNVPS
 FRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDRT
 DQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPPLR
 NPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVAA
 QHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL

Fig. 14B

1 cggaagccat ggagctcgag atctgattgc tggacacgga cggaactccg acgtatctcg
 61 cagatgcatg ttaacatttt acatccacaa ctgcaaacga tggctcgagca gtggcaaagt
 121 cgagaacgcc catcgctgga gaccgagaat ggcaaaggat cgctgctcct ggaaaatgaa
 181 ggtgtcgag ataatcatcac tatgtgtcca ttcggagaag ttattagtgt agtatttccg
 241 tggtttcttg caaatgtgag aacatcgcta gaaatcaagc tatcagattt caaacatcaa
 301 cttttcgaat tgattgctcc gatgaagtgg ggaacatatt ccgtaaagcc acaggattat
 361 gtgttcagac agttgaataa tttcggcgaa attgaagtta tatttaacga cgatcaaccc
 421 ctgtcgaaat tagagctcca cggcactttc ccaatgcttt ttctctacca acctgatgga
 481 ataaacaggg ataaagaatt aatgagtgat ataagtcatt gtctaggata ctactggat
 541 aaactggaag agagcctcga tgaggaactc cgtcaatttc gtgcttctct ctgggctcgt
 601 acgaagaaaa cgtgcttgac acgtggactt gaggttacca gtcactacgc gttccccgaa
 661 gaacagtact tgtgtgttgg tgaatcgtgc ccgaaagatt tggaaatcaa agtcaaggct
 721 gccaaagctga gttatcagat gttttggaga aaacgtaaag cggaaatcaa tggagtgtgc
 781 gagaaaatga tgaagattca aattgaattc aatccgaacg aaactccgaa atctctgctt
 841 cacacgtttc tctacgaaat gcgaaaattg gatgtatacg ataccgatga tctctcagat
 901 gaaggatggg ttcttcaatt ggctggacgt accacgtttg ttacaaatcc agatgtcaaa
 961 cttacgtctt atgatgggtg ccgttcggaa ctggaaagct atcgatgccc tggattcgtt
 1021 gttcgcgcgac aatcactagt cctcaaagac tattgtcgcc caaaaccact ctacgaacca
 1081 cattatgtga gagcacacga acgaaaactt gctctagacg tgctcagcgt gtctatagat
 1141 agcacaccaa aacagagcaa gaacagtgc atggttatga ctgattttcg tccgacagct
 1201 tcaactcaaac aagtttcaat ttgggacctt gacgcgaatc ttatgatacg gcctgtgaat
 1261 atttctggat tcgatttccc ggccgacgtg gatatgtacg ttcgaatcga attcagtgtg
 1321 tatgtgggga cactgacgct ggcacaaaaa tctacaacaa aagtgaatgc tcaatttgca
 1381 aatggaata aggaaatgta cacttttgat ctatacatga aggatatgcc accatctgca
 1441 gtactcagca ttcgtgtttt gtacggaaaa gtgaaattaa aaagtgaaga attcgaagtt
 1501 ggttgggtaa atatgtccct aaccgattgg agagatgaac tacgacaagg acaattttta
 1561 ttccatctgt gggctcctga accgactgcc aatcgtagta ggatcggaga aaatggagca
 1621 aggataggca ccaacgcagc ggttacaatt gaaatctcaa gttatggtgg tagagttcga
 1681 atgccgagtc aaggacaata cacatatctc gtcaagcacc gaagtacttg gacggaaact
 1741 ttgaatatta tgggtgatga ctatgagtcg tgtatcagag atccaggata taagaagctt
 1801 cagatgcttg tcaagaagca tgaatctgga attgtattag aggaagatga acaacgtcat
 1861 gtctggatgt ggaggagata cattcaaaag caggagcctg atttgctcat tgtgctctcc
 1921 gaactcgcat ttgtgtggac tgatcgtgag aacttttccg agctctatgt gatgcttgaa
 1981 aaatggaaac cgccgagtgt ggcagccgag ttgactttgc ttggaaaacg ttgcacggat
 2041 cgtgtgattc gaaagtgtgc agtgagagaag ttgaatgagc agctgagccc ggtcacattc
 2101 catcttttca tattgcctct catacaggcg ttgaagtacg aaccgcgtgc tcaatcggaa
 2161 gttggaatga tgctcttgac tagagctctc tgcgattatc gaattggaca tcgacttttc
 2221 tggctgctcc gtgcagagat tgctcgtttg agagattgtg atctgaaaag tgaagaatat
 2281 cgccgtatct cacttctgat ggaagcttac ctccgtggaa atgaagagca catcaagatc
 2341 atcaccgcgac aagttgacat ggttgatgag ctacacgaa tcagcactct tgtcaaagga
 2401 atgccaaaag atgttgctac gatgaaactg cgtgacgagc ttcgatcgat tagtcataaa
 2461 atggaaaata tggattctcc actggatcct gtgtacaaac tgggtgaaat gataatcgac
 2521 aaagccatcg tcttaggaag tgcaaaacgt ccgttaaatg ttcactggaa gaacaaaaat
 2581 ccaaagagtg acctgcacct tccgttctgt gcaatgatct tcaagaatgg agacgatctt
 2641 cgccaggaca tgcttgttct tcaagttctc gaagttatgg ataacatctg gaaggctgca

Fig. 15 (sheet 1 of 2)

2701 aacattgatt gctgtttgaa cccgtacgca gttcttccaa tgggagaaat gattggaatt
 2761 attgaagttg tgcctaattg taaaacaata ttcgagattc aagttggaac aggattcatg
 2821 aatacagcag ttcggagtat tgatccttcg tttatgaata agtggattcg gaaacaatgc
 2881 ggaattgaag atgaaaagaa gaaaagcaaa aaggactcta cgaaaaatcc catcgaaaag
 2941 aagattgata atactcaagc catgaagaaa tattttgaaa gtgtcgatcg attcctatac
 3001 tcgtgtgttg gatattcagt tgccacgtac ataatgggaa tcaaggatcg tcacagtgat
 3061 aatctgatgc tcactgaaga tggaaaatat gtccacattg atttcggtca cattttggga
 3121 cacggaaaga ccaaacttgg gatccagcga gatcgtcaac cgtttattct aaccgaacac
 3181 tttatgacag tgattcgatc gggtaaactc gtggatggaa attcgcgatga gctacaaaaa
 3241 ttcaaaacgt tatgcgtcga agcctacgaa gtaatgtgga ataatcgaga tttgttcgtt
 3301 tccttgttca ccttgatgct cggaatggag ttgcctgagc tgtcgacgaa agcggatttg
 3361 gatcatttga agaaaaccct cttctgcaat ggagaaagca aagaagaagc gagaaagttt
 3421 ttcgctggaa tctacgaaga agccttcaat ggatcatggt ctacccaaaac gaattggctc
 3481 ttccacgcag tcaaacta ctga

Fig. 15 (sheet 2 of 2)

Fig. 16

CONVERGENT TGF- β AND INSULIN SIGNALING
ACTIVATE GLUCOSE-BASED METABOLISM GENES

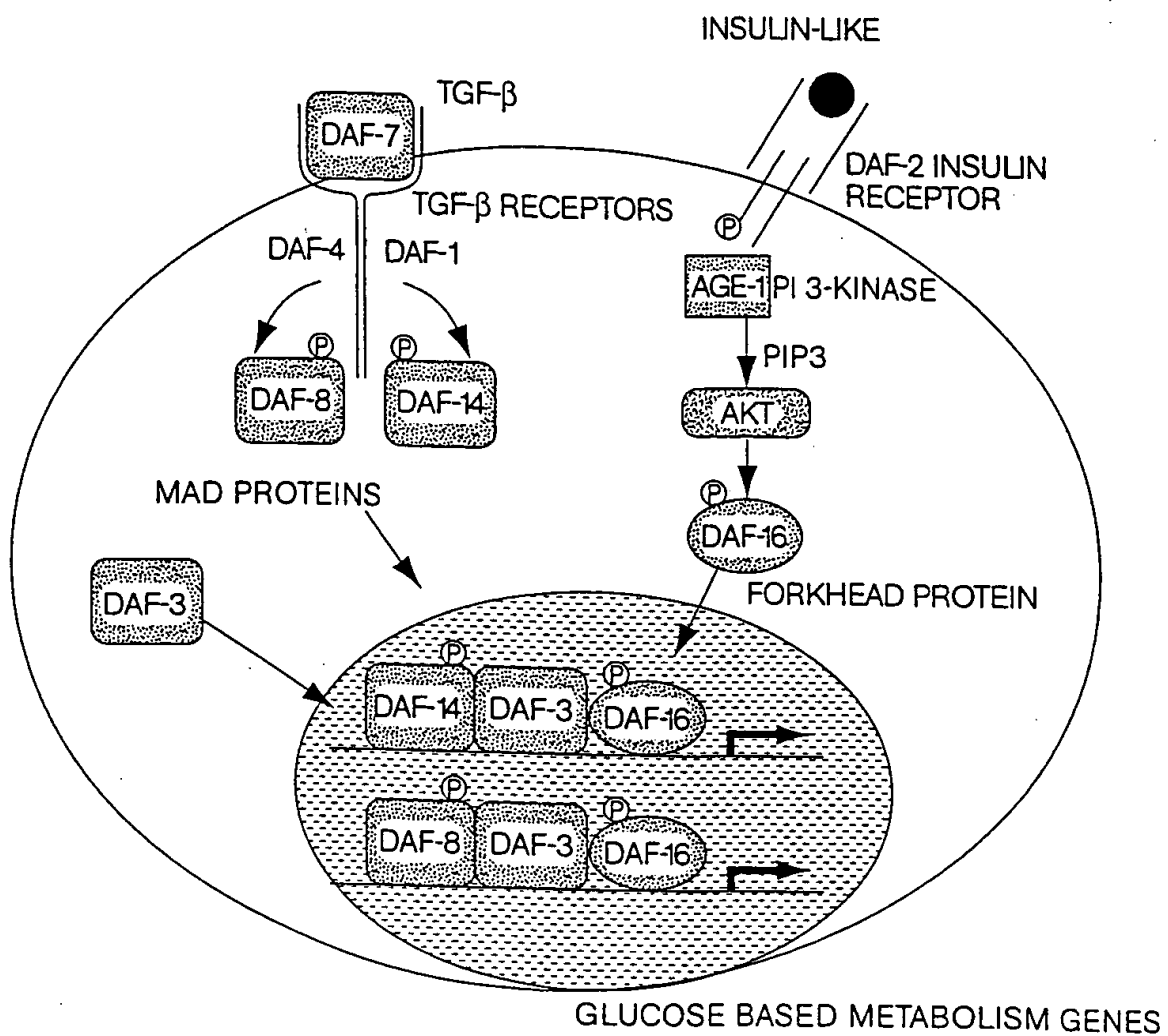
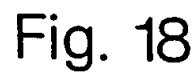
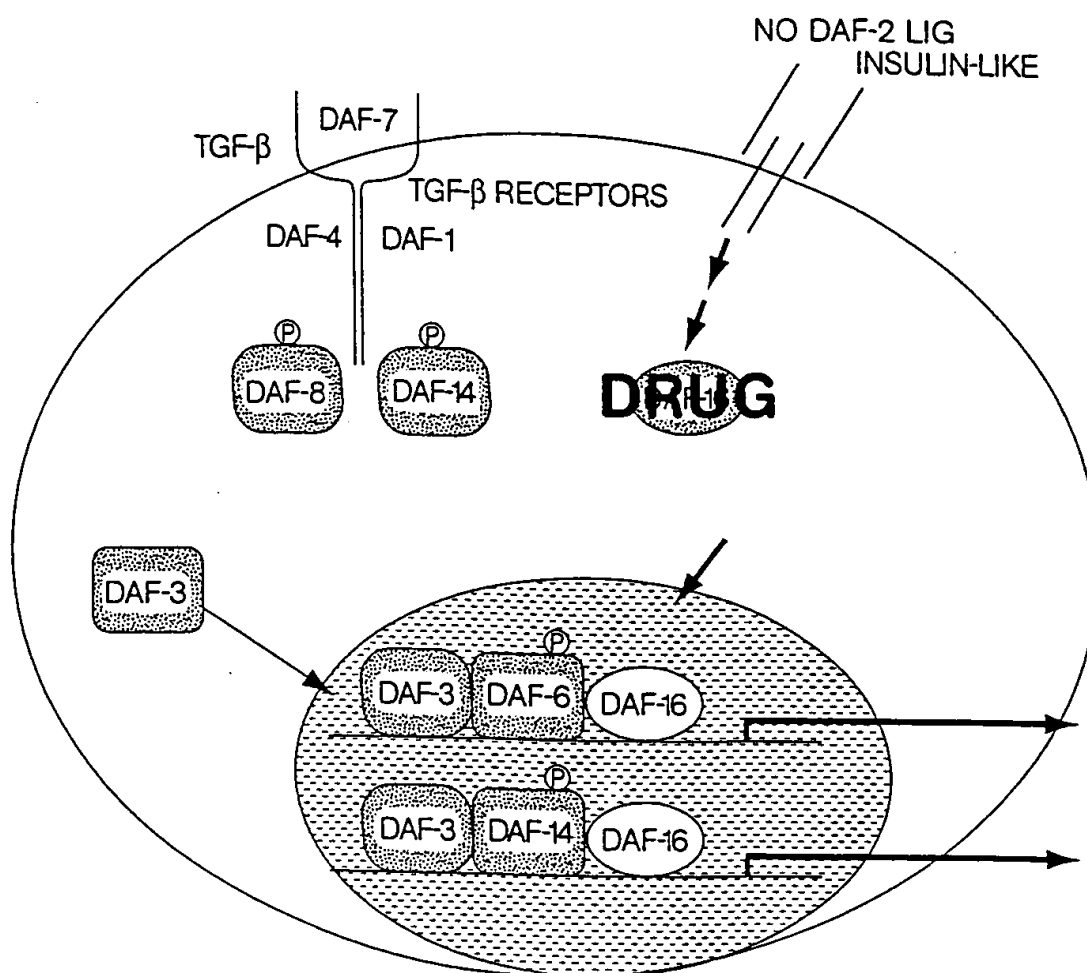


Fig. 17

NO DAF-2 LIG INSULIN-LIKE



DRUGS THAT INHIBIT DAF-16 OR DAF-3
(OR PROTEINS IN THE PATHWAY)
CAN BE DISCOVERED USING REPORTER GENES
BEARING THEIR COGNATE BINDING SITES



DRUG CAUSES A DECREASE IN DAF-16 ACTIVITY, ACTIVATING
THE REPORTER GENE LIKE A DAF-16 MUTANT.
THIS BYPASSES THE NEED FOR INSULIN

Fig. 19

DRUGS THAT INHIBIT DAF-3 WILL CURE
THE DIABETES CAUSED BY A LACK OF DAF-7

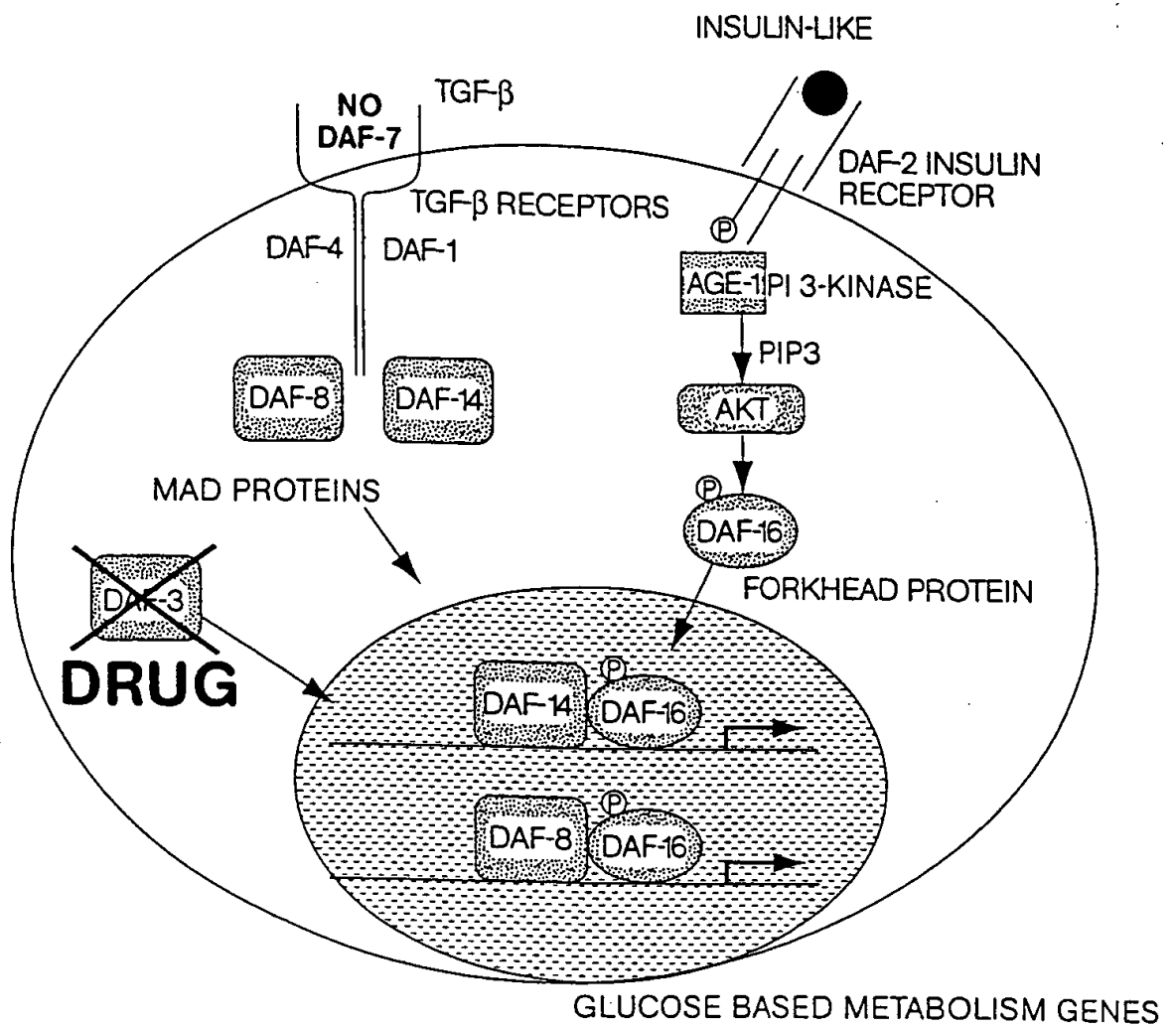


Fig. 20

DAF-16a1	1	-----MMEMLVDDQGTDASSBSASTSTSSVRFGA	DTFMNT	DDVMMNMDDMEFI	PRDR
DAF-16b	1	-----MNDSDDDDFEPRGCAWTWPMQOYIYQESB	ATIPHHHLNQHNNHYHPMH	HHQLPHMQQLP	QELLN
FKHR	1	-----MAEAPQVVEIDPDFELPRPRSC	TWPLRPFETQSNKATSESNL	SGBAAN	-----PDAAAGLESASA
FKHRL1	1	MAEAPASPAPLSPELEVELDPEFEFQSRPRSC	TWPLQRPQLCAPAKP	EGETAADSMIE	-----EEDDEDEDGGG
AFX	1	-----MAEAPASPAPLSPELEVELDPEFEFQSRPRSC	TWPLQRPQLCAPAKP	EGETAADSMIE	-----MRIQEQKAA
DAF-16a1	52	CN..TWPMRRRPPLEPPNLSPIIHEQIPEEDADLYCSNEQ	..CCQLCGABSNCSTAM	HTPDGNSH	QTSFFSDFRMSE
DAF-16b	68	LNMUTLTSBSSSVASSIGGACSGSSTAATN	SSQOQTVQCM	LAASVECS	SSGMTLGMSENLSQGGGPMFAKKR
FKHR	64	RAVSADFMNLSLLESEDEFQAPGSVAAAVAA	AAAAAATGGLCGDF	QGP	EAGCLHBAAPPEPPFPPLSQHPVFPFAAA
FKHRL1	72	RAGSAMAI	GGGSGT	LGSGLL	EDS..ARVLAPGCGQDPGSGPATAAGGLSGGT
AFX	10	AIIDLDFDFEFQSRPRSC	TWPLPREETIANQ	PSEPPEVEPD	CEKVHTECRSEI
DAF-16a1	127	SPDDTVSGKKTTRRNAGNM	SYAELITTA	MA	SPEKRLTLAQVYEMVQNVYFRDKGDSNSSAGWKNSIRHNLSLHSHR
DAF-16b	148	CRKKP	TDQLAOKPNWGEESYS	DI	IAKALASAPDGRKLNEIYQWFS
FKHR	143	GELAGQPRKSSSRRNAGNLSYADLITKA	IESBAEKRLT	LSQIYEMVKS	VPYFKDKGDSNSSAGWKNSIRHNLSLHSHK
FKHRL1	143	G..SGOPRK	CSSRRNAGNLSYADLITRA	IESBPD	KRLTLSQIYEMVRCVYFKDKGDSNSSAGWKNSIRHNLSLHSHR
AFX	86	GPRKGGSRNAGN	QSYAEFIS	QIESAPEKRLTLAQIYEMVTVYFKDKGDSNSSAGWKNSIRHNLSLHSHK
DAF-16a1	207	FMRIQNEGAGKSSWVWV	INPDAPKPGNRPR	TRERSNT	IEETTAKQLEKERRGAKKRIKRALMGSLHSTLNCNSIAGSIQT
DAF-16b	227	FMRIQNEGAGKSSWVWV	INPDAPKPGNRPR	TRERSNT	IEETTAKQLEKERRGAKKRIKRALMGSLHSTLNCNSIAGSIQT
FKHR	223	FIRVQNEGTGKSSWMLN	INPEG..GKSGKSP	RRRAASMDNNSK	FAKRSRAAKK.....AS.LQSGQEGA.GDSPGSQ
FKHRL1	220	FMVQNEGTGKSSWMLN	INPDG..GKSGKAP	RRRAVSMDNSK	YTKSRGRAAKK.....AA.LQTAPESA.DDSP.SQ
AFX	160	FTKVHNEATGKSSWMLN	INPEG..GKSGKAP	RRRAASMDSSK	LLRGRSKAPKK.....PSVLPAPPEGATPTSPVGH
DAF-16a1	287	ISHLDYDDDSMQCAF	DNVPSSFRPR	TQSNLSIPGSS	SRVSPAIGSDIYDDL.EFSPMVGESVPAIPSDIVDRTDQMRIDA
DAF-16b	307	ISHLDYDDDSMQCAF	DNVPSSFRPR	TQSNLSIPGSS	SRVSPAIGSDIYDDL.EFSPMVGESVPAIPSDIVDRTDQMRIDA
FKHR	292	FSKPASPGSHSND	DFDNWSTFR	TSSNAS..TISGR	LSPIM.TEQDDLGECD.VHSMVYPPSAAKMAST.....
FKHRL1	288	LSKWPSPSTRSS	DELDAWTFR	SRTNSNAS..TVBGR	LSPIMASTELDEVODDDAPLSPLMYSASLSPSVSKPCTVE
AFX	231	FAKWSGSP	CSRNRE	ADMMTFR	PRSSSNAS..SVSTRLSPLRPESEV.LAEI
DAF-16a1	366	THIGGVQIKQESKPIKTE	PIAPP	PSYHELNSVRG	SCAQNPLLRNP
DAF-16b	386	THIGGVQIKQESKPIKTE	PIAPP	PSYHELNSVRG	SCAQNPLLRNP
FKHR	359	LPSSLSEISNPENM	ENLLDNL	NLLSSPT	SLTVSTQSSPGTMMQOTPCYEFAPP.NTSLNSPSPNYQKYTYGQSSMSPLP
FKHRL1	366	LPRLTDMAGTM	NLDGLTENLMD	DLNITLPP	SPSPTCGLMQRSSSFYTTK.GSGLGSP
AFX	308	LTSSHLLSRG	LSGFSLOHPGV	TGPLHTYSS	SLFSPAECP
DAF-16a1	446	SPLPGIQS..CGI	VAAQHTVASS	BALPID	LENLTLPPDQPLMDTMDVDA
DAF-16b	466	SPLPGIQS..CGI	VAAQHTVASS	BALPID	LENLTLPPDQPLMDTMDVDA
FKHR	436	QMPIQTLQDNK	SSYGGMSQ	YNCA	PGLLKEHLLTSDSEPHNDI.WTPVD
FKHRL1	445	QSPMQTIQENK	PATFSSMSHY..GNQ	TLOD	LLTSDLSHSDVMMTQSDPLMSQASTAVSAQNSRRNVMLRNDPMMSFAC
AFX	388	QAE	TLLGLLPSE...	SKLATGV	GCCKP
DAF-16a1	511	-----	-----	-----	-----
DAF-16b	531	-----	-----	-----	-----
FKHR	511	ASHNKMMPSSH	TEPGHAQ	QTS	VNCRPLPHTVSTMPHTSGMNR
FKHRL1	523	PNQGLVN	ONL	LEHQH	QTCGALGSRALNSVBNM
AFX	464	QDL	LD	MYMEN	LECDMDNIISDLMDE

FIG. 21A-1

DAF-16a1	511	-----
DAF-16b	531	-----
FKHR	590	MGLLHQEKLPDLD.GMFIERLDCDMESIIRNDLMDGPTLDFNFDNVLENC.....SEPHSVKTTTHSWVSG
FKHRL1	599	LPVMGHEKFPDLDLDMFNGSLECDWESIIRSELMADAGLDFNFDLSLSTCNVVGLNVGNFTGAKQASSQSWVPG
AFX	502	-----

FIG. 21A-2

Fork head Domain Alignment (*C. elegans*, human, others)

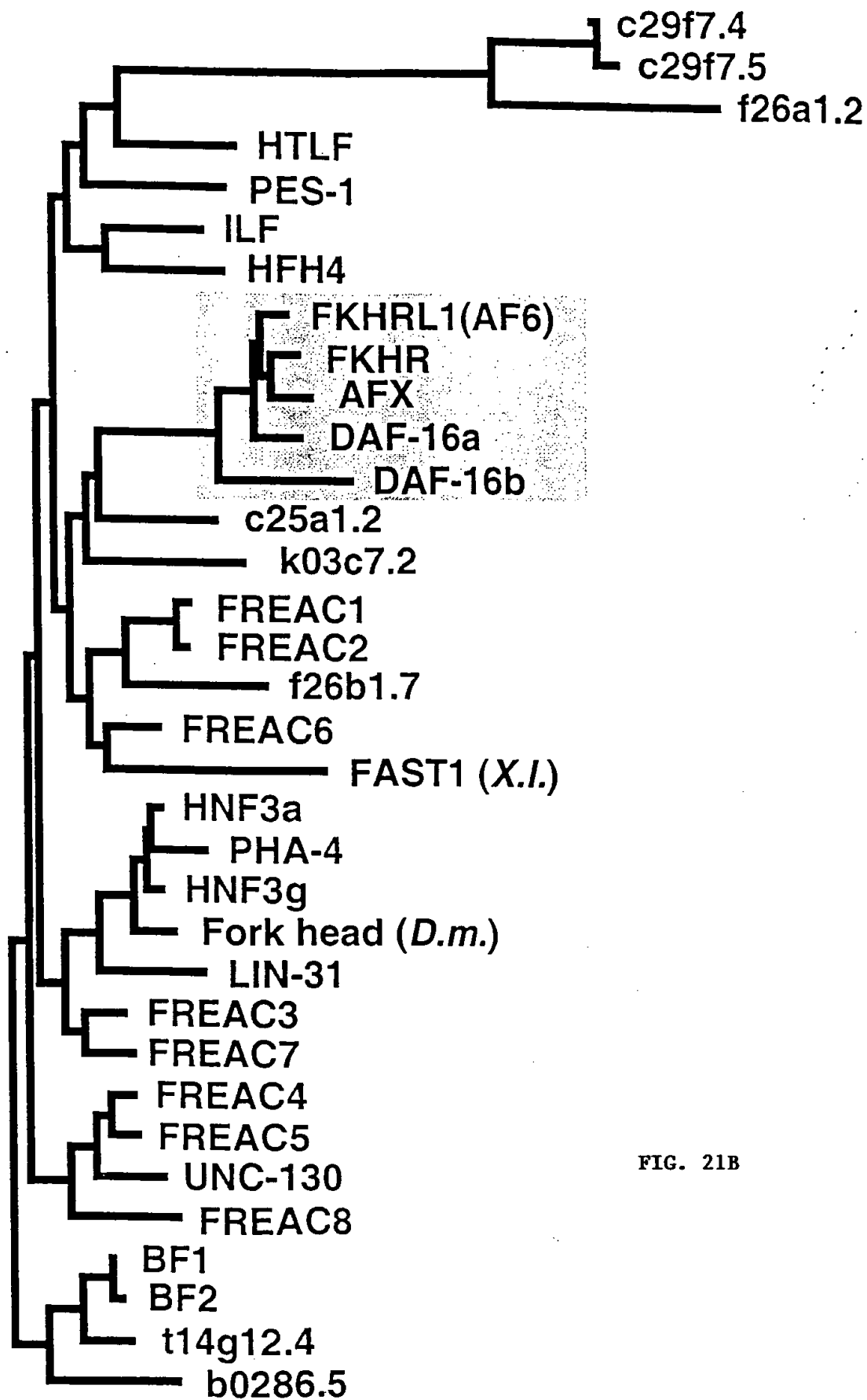


FIG. 21B

09963692.092504
105250-2592960

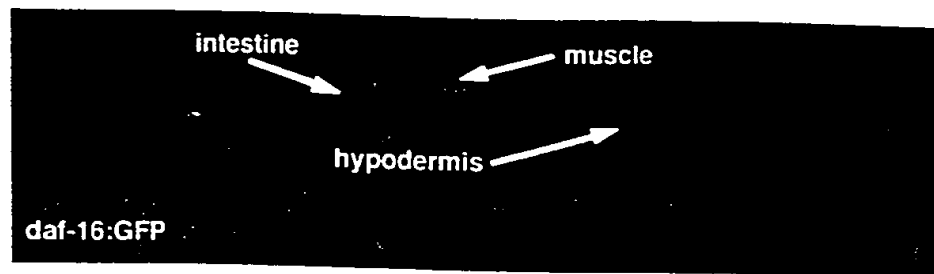


Fig. 22

INJECTION OF OF DAF-7 BYPASSES OBESITY-INDUCED DEFECTS IN INSULIN-REGULATION OF METABOLISM

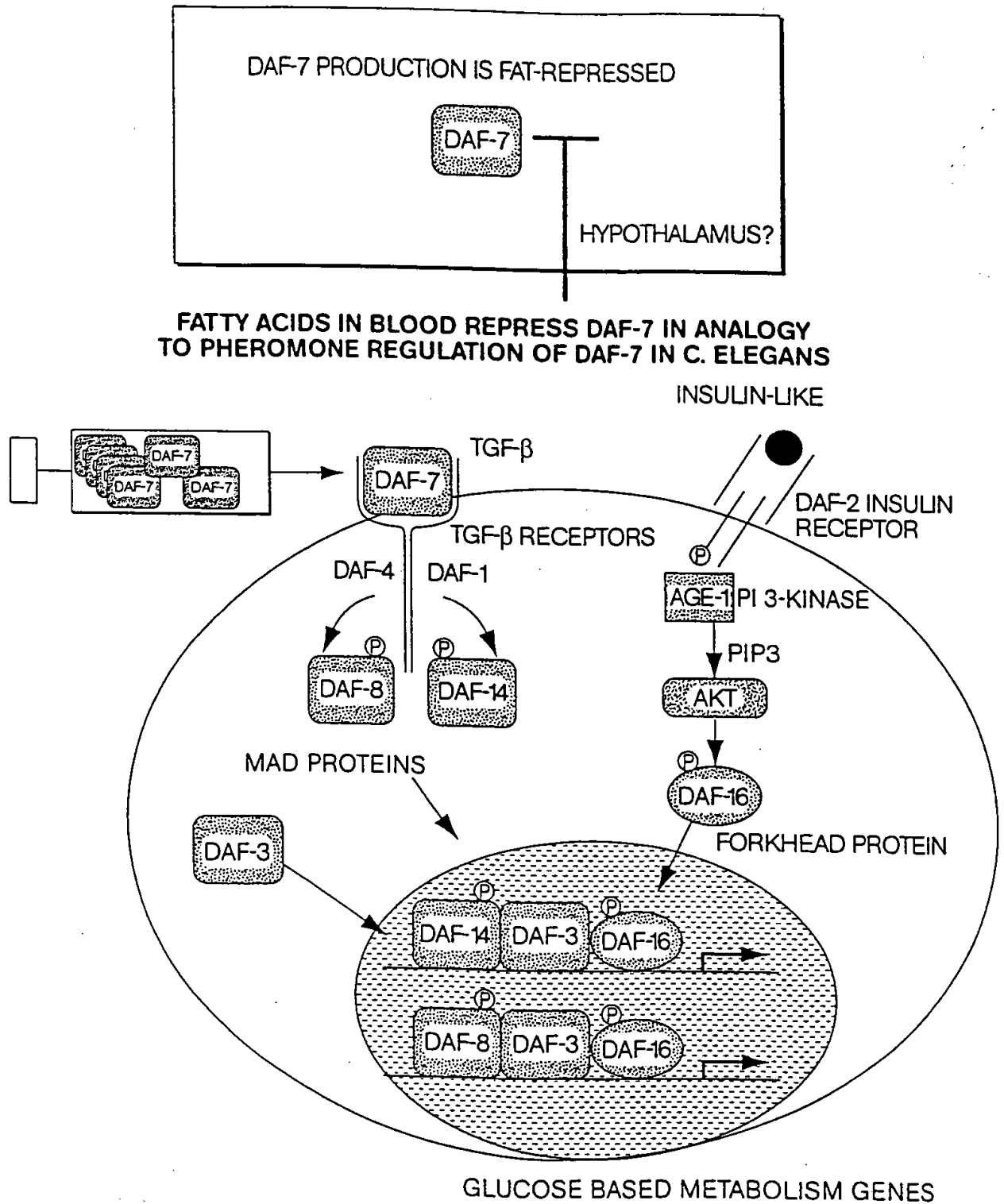


Fig. 23

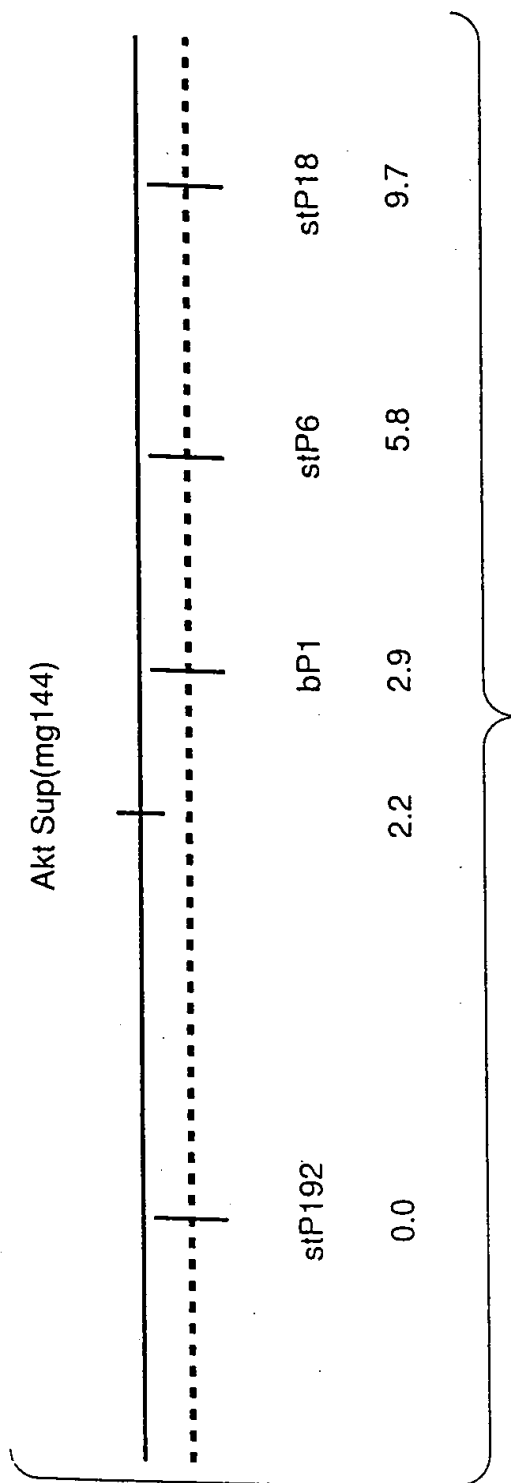


Fig. 24

Comparison of the human AKT protein sequence to the cosmid sequence
C12D8, located in the genetic interval where sup(mg144) maps. Numbering in the AKT
protein sequence by amino acid residues, and in the cosmid sequence by nucleotide
position.

Score = 450 (207.4 bits), Expect = $5.2e-165$, Sum P(7) = $5.2e-165$
Identities = 79/121 (65%), Positives = 97/121 (80%), Frame = +1

Query: 319 EVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFELILMEEIRFPRTLGPPEAKS 378
+VL+D+DYGR VDWVG+GVVMYEMMCGRLPFY++DH KLFELI+ ++RFP L EA++
Sbjct: 33685 QVLDDHDYGRCDWVGWGVVMYEMMCGRLPFYKDHNLKLFELIMAGDLRFPSKLSQEART 33864

Query: 379 LLSGLLKKDPTQRLGGGSEDAKEIMQHRFFANIVWQDVYERKLSPPFKPQVTSETDTRYFD 439
LL+GLL KDPTQRLGGG EDA EI + FF + W+ Y K++ PP+KP V SETDT YFD
Sbjct: 33865 LLTGLLVKDPTQRLGGGPEDALEICRADFFRTVDWEATYRKEIEPPYKPNVQSETDTSYFD 34047

Score = 256 (118.0 bits), Expect = $5.2e-165$, Sum P(7) = $5.2e-165$
Identities = 48/66 (72%), Positives = 59/66 (89%), Frame = +1

Query: 146 TMNEFEYLKLLGKGTFGKVILVKEKATGRYYAMKILKKEVIVAKDEVAHTLTENRVLQNS 205
TM +F++LK+LGKGTFGKVIL KEK T + YA+KILKK+VI+A++EVAHTLTENRVLQ
Sbjct: 32314 TMEDFDLKVILGKGTFGKVILCKEKRTQKLYAIKILKDVIIAREEVAHTLTENRVLQRC 32493

Query: 206 RHPFLT 211
+HPFLT
Sbjct: 32494 KHPFLT 32511

Score = 190 (87.6 bits), Expect = $5.2e-165$, Sum P(7) = $5.2e-165$
Identities = 36/45 (80%), Positives = 37/45 (82%), Frame = +2

Query: 276 KLENLMLDKDGHIKITDFGLCKEGIKDGATMKTFCGTPEYLAPEV 320
KLENL+LDKDGHIKI DFGLCKE I G TFCGTPEYLAPEV
Sbjct: 33509 KLENLLLDKDGHIKIADFGLCCKEISFGDKTSTFCGTPEYLAPEV 33643

Score = 188 (86.7 bits), Expect = $5.2e-165$, Sum P(7) = $5.2e-165$
Identities = 37/57 (64%), Positives = 42/57 (73%), Frame = +3

Query: 209 FLTALKYSFQTHDRLCFVMEYANGGELFFHLSRERVFSEDRARFYGAIEIVSALDYLH 265
+ LKYSFQ LCFVM++ANGGELF H+ + FSE RARFYGAIEIV AL YLH
Sbjct: 32667 YFQELKYSFQEQHYLCFVMQFANGGELFTHVRKCGTFSEPRARFYGAIEIVLALGYLH 32837

Score = 166 (76.5 bits), Expect = $5.2e-165$, Sum P(7) = $5.2e-165$
Identities = 29/59 (49%), Positives = 42/59 (71%), Frame = +1

Query: 53 NNFSVAQCQLMKTERPRPNTFIIRCLQWTTVIERTFHVETPEEREWEATAIQTVDGLK 111
+ F++ Q M E+PRPN F++RCLQWTTVIERTF+ E+ E R+ W AI++++ K
Sbjct: 31846 STFAIFYFQTMLEKPRPNMFMVRCLQWTTVIERTFYAESAEVRQRWIHAIESISKKYK 32022

Score = 134 (61.8 bits), Expect = $5.2e-167$, Sum P(8) = $5.2e-167$
Identities = 24/33 (72%), Positives = 30/33 (90%), Frame = +3

Query: 210 LTALKYSFQTHDRLCFVMEYANGGELFFHLSRE 242
L LKYSFQT+DRLCFVME+A GG+L++HL+RE
Sbjct: 33156 LQELKYSFQTNDRLCFVMEFAIGGDLYYHLNRE 33254

Expression of AKT:GFP in daf-2 dauers



Fig. 26A

Expression of AKT:GFP in N2 adult

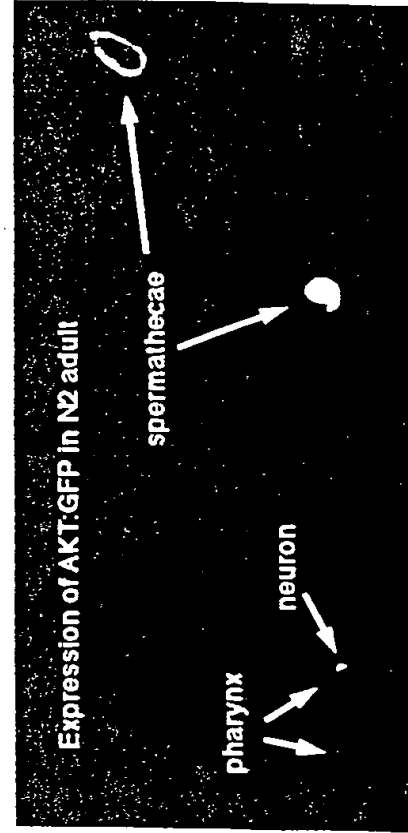
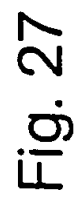


Fig. 26B



	1	15 16	30 31	45 46	60	
1 ZK84.6	-MNSVFTIIFVLCAL	QVAASFRQSGF---	P SMSEESASMQLLREL	QH--NMESAHRPMP	54	
2 ZK75.1	-MFSFFT-YFLLSAL	LLSASCRQ-----	P SMDT-SKADRILREI	E----METELENQLS	47	
3 ZK1251.2	----MPPIILVFFLV	LIPASQQY-----	P FSLE-SLNDQIINEE	VI--EYMLENSIRSS	47	
4 C06E2	--MIVTLIVFLVIGL	QMAHLSQVSGNNENG	FLNP-FDLSQWSEEI	LHRQYHHHHHHHHCN	57	
5 ZK75.2	----MNAIIFCLLET	TVTATYEVF-----	G KGIEHRNEHLIINQL	D---IIPVESTPTPN	48	
6 ZK75.3	MKLSVVLALFIIFQL	GAASLMRN-----	W MFDFEKELEHDYDDS	E---IGFHNHLSLMA	51	
7 C17C3	-----	-----	-----	MKLLHI F---IIFLLFQSCSN	18	
8 F13E12	-----	-----	-----	MYWFRQVYRPS FF--FGFLAILLLSS	50	
9 INSULIN	-----	-----	-----	MA LWMRLPLLLALLALW	17	
CONSENSUS	-----	-----	-----	-----		

	61	75 76	90 91	105 106	120	
1 ZK84.6	RARRVPAPGETRACG	RKLISLVMVAVCGD-L	CN-----	-----	85	
2 ZK75.1	RARRVPA-GEVRACG	RRLLLFWWSTCGE-P	CT-----	-----	77	
3 ZK1251.2	RTRRVPDEKKIYRCG	RRIHSYVFAVCGK-A	CE-----	-----	78	
4 C06E2	RARRTLETEKIYRCG	RKLYTDVLSACNG-P	CE-----	-----	88	
5 ZK75.2	RASRVQK----RLCG	RRLILFMLATCG--E	CD-----	-----	74	
6 ZK75.3	RSRRGDK---VKICG	TKVLKMVMVMCGG-E	CS-----	-----	79	
7 C17C3	KMCQYSK-KKYKICG	VRALKHMKVYCTR-G	MT-----	-----	48	
8 F13E12	PTPSDAS---IRLCG	SRLTTTLLAVCRNQL	CTGLTAFKRSADQSY	APTTRDLFHIHHQO-	80	
9 INSULIN	GPDPAAAFVNQHLCG	SHLVEALYLVCGERG	FFYTPKTRREAEDLQ	VGQVELGGPGAGSL	77	
CONSENSUS	-----CG	-----C	-----	-----		

B CHAIN

C PEPTIDE

	121	135 136	150 151	165 166	180	
1 ZK84.6	-----PQEGKDIA	TECCGNQCSDDYIRS	ACCP-----	112		
2 ZK75.1	-----PQEDMDIA	TVCCTTQCTPSYIKQ	ACCPEK---	106		
3 ZK1251.2	-----SNTEVNIA	SKCCREECTDDFIRK	QCCP-----	105		
4 C06E2	-----PGTEQDLS	KLCCGNQCTFVEIRK	ACCADKL--	118		
5 ZK75.2	-----TDSSDLS	HICCIKQCDVQDIIR	VCCPNSFRK	106		
6 ZK75.3	-----S-TNENIA	TECCEKMCTMEDITT	KCCPSR---	107		
7 C17C3	-----R-DYGKLL	VTCCSKGCNAIDIQR	ICL-----	73		
8 F13E12	-----KRGGIA	TECCEKRCSFAYLKT	FCCNQDDN-	109		
9 INSULIN	QPLALEGSLQKRGIV	EQCCTSICSLYQLEN	YCN-----	110		
CONSENSUS	-----CC--C	-----C	-----C	-----		

A CHAIN

Fig. 28

Zk75-1	ACGRRRL	WSTCGEPCTx	xxQEDMDI	AT	VCC	TTQ	CTPS	YTKQAC	46
Zk84-6	Aggrk	maVgdlcnx	xxqegkd	lat	ecg	gnq	csdd	Yrsac	46
Zk1251-2	RCCRR	FAVCGKACEx	xxSTEVNI	AS	KCC	REE	CTDD	FIRKQ	46
C06e2	RCCRK	LSACNGPCEX	xxGTEQDL	SK	LCC	GNQ	CTFV	EIRKAC	46
Zk75-3	ICGTK	MVMCGGECsx	xxSTNENI	AT	ECC	EKM	CTME	DTTKC	46
Zk75-2	lggr	latqgecdtx	xxDSSEDL	SH	ICC	IKq	cdvq	dlirvc	46
Ins-Human	LCCSH	YLVCGERGFx	xxLQKR	IVE	QCC	TSI	CSLY	QLENYC	46
Ins-Rabbit	lggsh	YLVCGERGFx	xxtpksg	ive	qcc	tsi	csly	qlenyc	46
Ins1-Xenopus	lggsh	YLVCGdrGFx	xxkmkr	give	qcc	hst	csly	qlenyc	46
Ins2-Xenopus	lggsh	YLVCGdrGFx	xxkmkr	give	qcc	hst	csly	qlenyc	46
Ins-Alligator	lggsh	YLVCGdrGFx	xxspksg	give	qcc	hnt	csly	qlenyc	46
Ins-Elephantfish	lggsh	YLVCGdrGFx	xxpkqig	ive	qcc	hnt	csly	qlenyc	46
Igf1-Bovine	LCGAE	QFVCGDRGFx	xxAPQTGI	VD	ECC	FRS	CDLR	RLEMYC	46
Igf1-Dog	lggae	qfvCGdrGFx	xxapqtg	ivd	ecc	frs	cdlr	rlemyc	46
Igf2-Horse	lgggl	qfvCGdrGFx	xxrrsrg	ive	ecc	frs	cdla	lletyc	46
Igf2-Human	LCCGEL	QFVCGDRGFx	xxRRSR	GIVE	ECC	FRS	CDLA	LLETYC	46
Ilp-Amphioxus	YCCSTL	SFVCCGNRGYx	xxRRRR	CGIVE	ECC	YNV	CDYS	QLTESY	46
Lirp-Locust	YCCRH	KLVCRCGNYNx	xxRRTR	CGVFD	ECC	RKS	CSIS	ELQTYC	46
Bxa4-Bommo	YCCRH	ADLCWEAGVx	xxRGKR	GIVD	ECC	LRP	CSVD	VLLSYC	46
Bxb1-Bommo	YCCRH	ADLCFVGEKx	xxRGKR	CGVVD	ECC	FRP	CTLD	VLLSYC	46
Bxrpa-Hornworm	YCCRH	adlcpnvveyx	xxgkrag	vad	ecc	vnsc	tmd	vllsyc	46
Bxa1-Silkworm	YCCRR	sfvcdnqyqxx	xxgkrqg	glae	ecc	knpc	cten	ellgyc	46
Bxa2-Silkworm	YCCRR	LYVCDNQYQx	xxGKRQ	GIVE	ECC	NKP	CTEN	ELLGYC	46
Bax3-Silkworm	YCCRR	syicdnqylyx	xxgkrqg	glae	ecc	knpc	cted	ellgyc	46
F13b12	LCCSRL	LAVCRNQLCx	xxQKRQ	GIA	ECC	EKR	CSFA	YLLKTE	46
Mpi3-Seasnail	LCCSTL	QWLCSTYTTx	xxESRP	SIVC	ECC	FNQ	CTVQ	ELLAYC	46
Relaxin-Human	LCCREL	IAICGMSTWx	xxRPYV	ALFE	ECC	LIG	CTKR	SLAKYC	46
Rlf-Human	lgghh	vrVCGgprrwx	xxaaatn	par	YCC	lsg	ctqq	dlitlc	46

Fig. 29

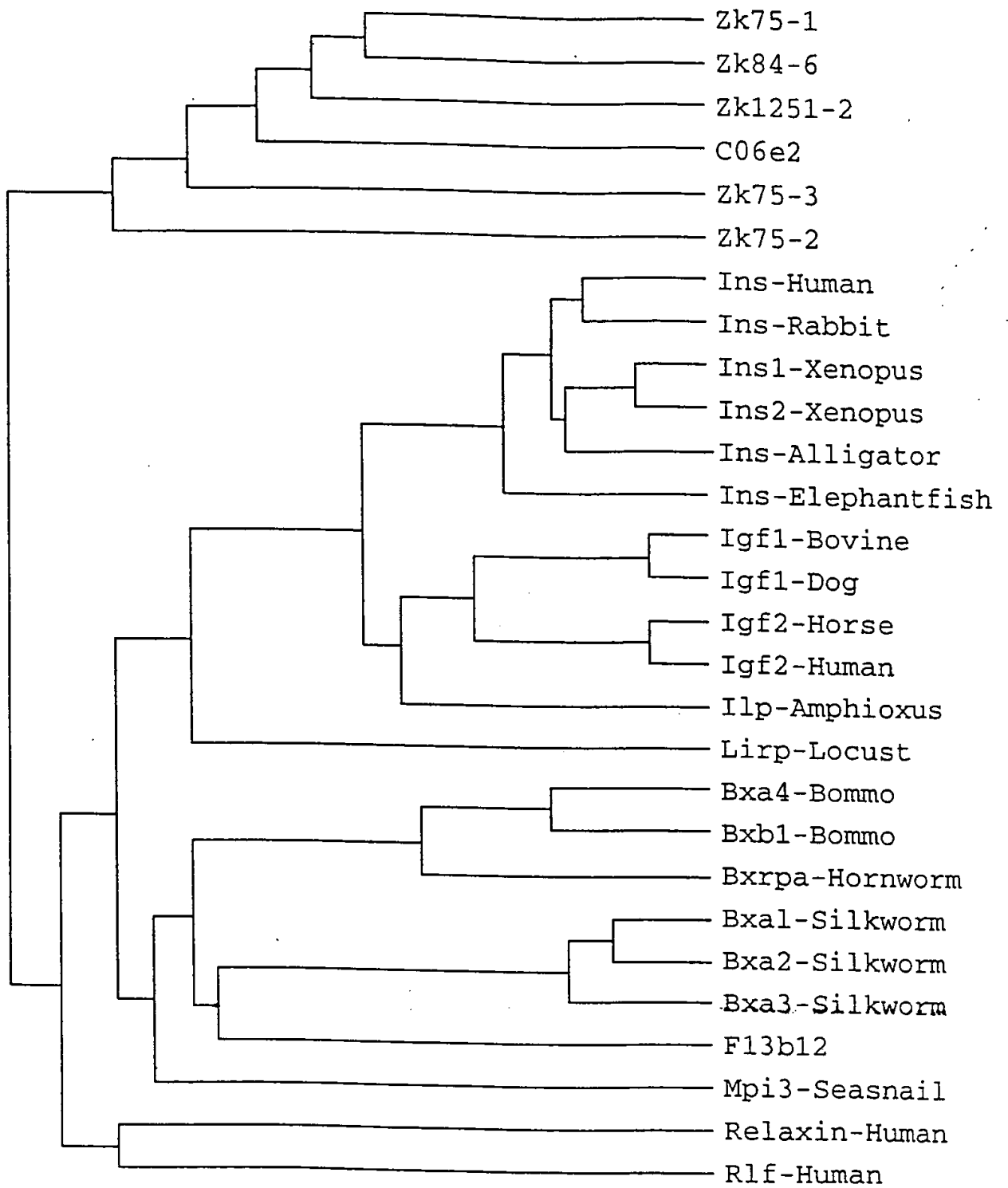


Fig. 30

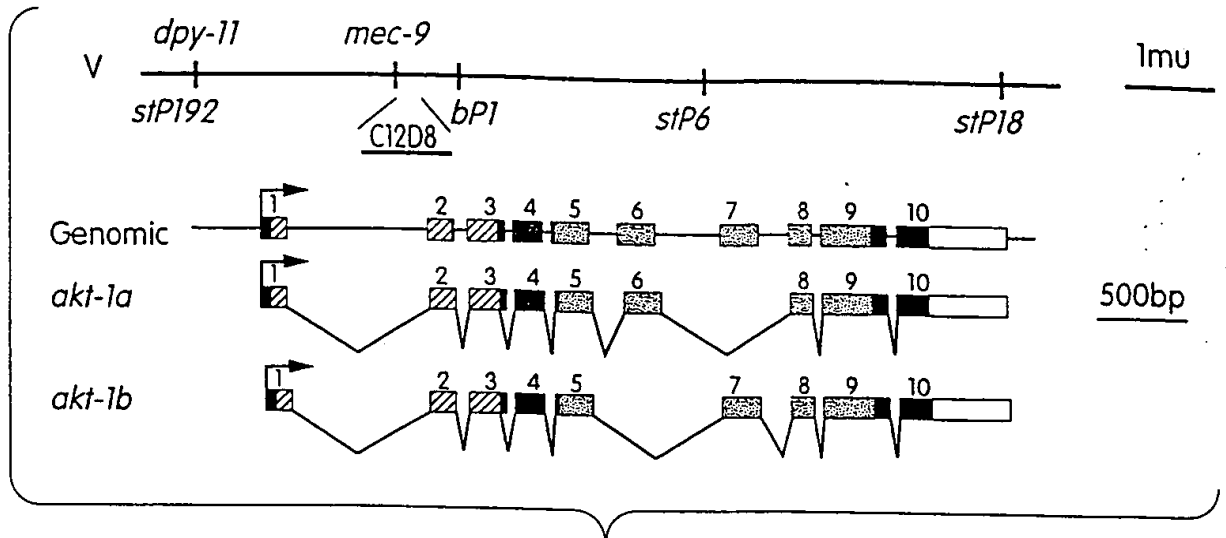


Fig. 31

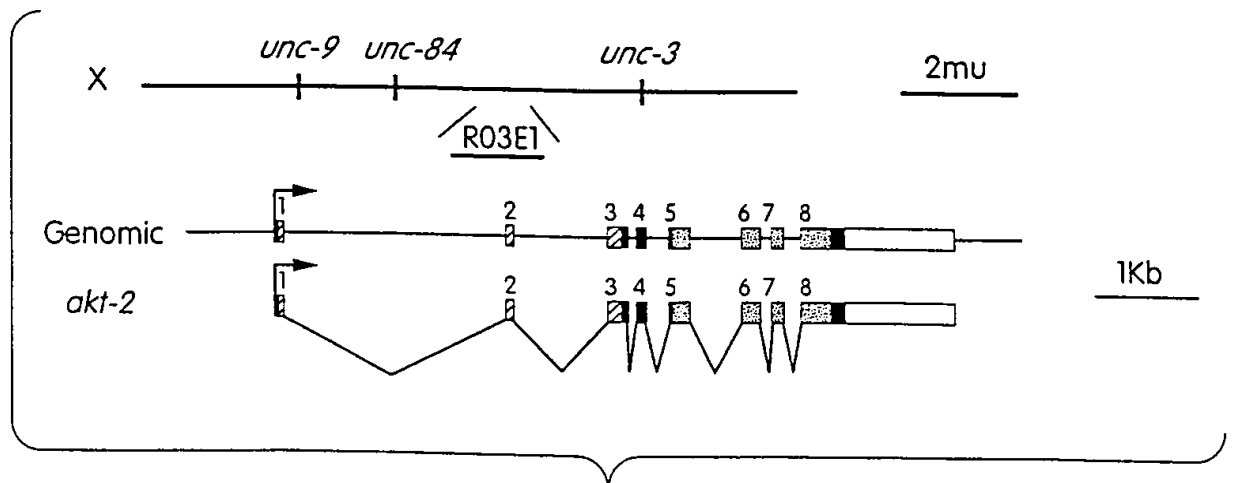


Fig. 32

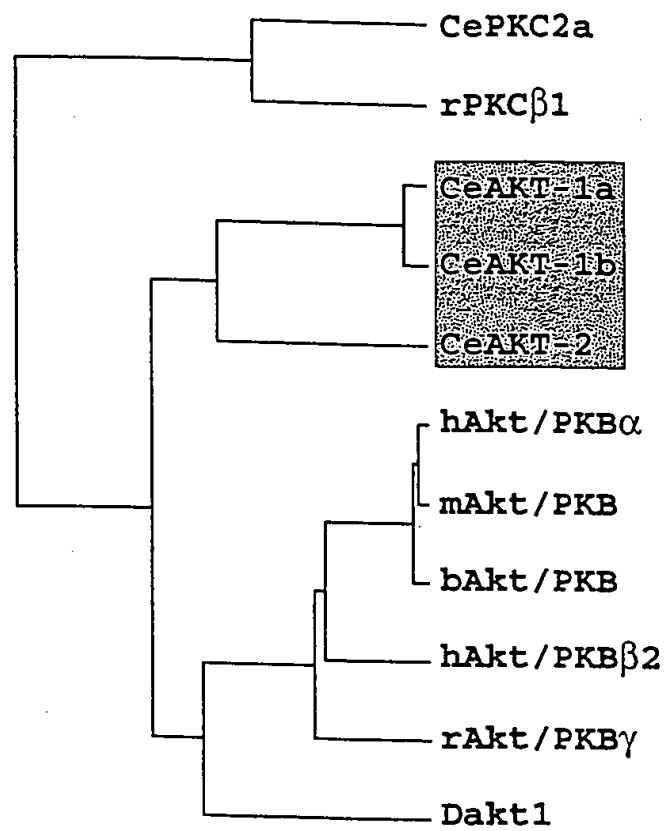


Fig. 33

AKT-1a MSMTSLSTKSRR--QEDVVIEGWLHKKGEHFRNWRPRYFMIFNDGALLGFRAKPKGQPFPEPL
 AKT-1b
 AKT-2 M..ENAHLOK..I..S.....IL R T...S...D..L
 hAkt/PKBa MSDVAT K...R..Y..KT...LLK...TFI..YKER..QDVDQREA

AKT-1a NDFMIKDAATMLFEKPRPNMFMVRCLQWTTVIERTFYAESAEVRQRWIHALESIS--KRYKGTN
 AKT-1b
 AKT-2 N..R...VCLD...I.....D..DF...E..QAV..SHNRL..ENA
 hAkt/PKBa N..SVAQCQL..KT R...T..II.....HV TP E..EE..TT..QTVADGL..KQE--

AKT-1a ANPQEELMETNQPKIDEDSEFAGAAHAIMGQPSSGHGDNCSIDFRASMISIADTSEAAKRDKI mg144 T
 AKT-1b
 AKT-2 G.TSMQEEED..GN.SGES.VNM-----DAT.TRS....ESTVMN.DEPE.VPRKNTV
 hAkt/PKBa -----E.EMD.-----R.GSPS..SGAE-----EMEV.L.KPKHRV

AKT-1a TMEDFDFELKVLGKGTGKVLGCKEKRTQKLYAIKILKKDVI PAREEVAHTLTENRVLQRCCKHPF
 AKT-1b
 AKT-2 ..D.....Q.....R..SSD.....IR..EMVVD..S.....YA..V
 hAkt/PKBa ..NE..EY..L.....V...A..GRY..M.....E..V..KD.....NSR...

AKT-1a LTELKYSEFQEQHYLCFVMOFANGGELEFTHVRK----CGTFSEPRARFYGAIEIVLALGYLH-RC
 AKT-1b TNDR...E..I..D..YY..LNREVQMNKEG.....S.....-AN
 AKT-2 L...A..YHL...E.....LQR-----K...A..T...S..I.....-HR
 hAkt/PKBa A...THDR...EY...F..LSRE-----RV...D.....S..D...SEK

AKT-1a DIVYRDMKLENLLELDKDGHIKTADEGLCKEEISFGDKTSTFCGTPEYLAPEVLDDHDYGRVCDW
 AKT-1b S...L.....
 AKT-2 N.....R.....T.....KY.....IE..I..D..S
 hAkt/PKBa NV...L...M.....T.....G..KD..ATMK.....E..N...A...

AKT-1a WGVGVVYEMMCGRLPFYSKDHNLKLELIMAGDLRFPSKLSQEARTLLETGLLVKDPTQRLGGGP
 AKT-1b
 AKT-2SA..ENG.....TTC..K..NR..P..V...S...ERV..AK...A..
 hAkt/PKBa L.....NQ..E.....LMEEI...RT..GP..KS...S...K...K...S

AKT-1a EDALEICRADFFERTVDWEATYRKEIEPPYKPNVQSETDTSYFDN-EFTSQPVQLTPPSRSGALA
 AKT-1b
 AKT-2 D..R..VS..E..KD.....L...V...F...M.....F..RVRV..ILLKV-----E..I
 hAkt/PKBa ..K..MQHR..AGIV.QHV..E..KLS..F..Q..T.....R...E...A..MITI...DQDDSM

AKT-1a TVDEQEEMQSNFTQFSFHNVMGSINRIHEASEDNEDYDMGZ
 AKT-1b
 AKT-2
 hAkt/PKBa C...-S..RRPH..P...YSASSTA

Fig. 34

cataaaatccagtaaatggtaaaattttcaatccatctcgatggaggatctcacccaactaacacgtcgctcgacaccacaactac
 taacaatgacacgacatcggtcgatgaagcggcgccaacgggtgaggaactagtttctagacgaacatcggaatgcggcttaaagttcgggtgcac
 ttatcaaaactagaccggttttttagaccctctttcaaagcggggaactgcaatacactttttgaacctaaaacctagatttttggtgttctaaat
 tcttttgtaattggagagccaattcaaccggaactctttttatagggaaaacggttttgcacgtagcagataagttaaatagaaaatattt
 taaaatatttttttgtctaggaaaaattgataaagcacctggccaattttcagaacgttccaattttacctacaatacaaaattggccggca
 agcttatggcttctgtttgcctacttctagcttgaaacattctaaaggtcgcgtagcgaaaaaatttttaggcttttttaataaatgtttggg
 ccggaacacttaaccgaatagcatgatgaaacgctctaaaacttgaaattgaaaatttcagttgatgcttttaataaaaagttttgaggtttca
 cctgcctaagatcggttttagcataaattgtagatgaccgagagtatacaattaaatattaataatgaatttcgaaatatgaattttggtt
 gacttccattatgtttttttttcacattttacaactattctaggcaaaaatgaaaaaaaacttgtagaataattttcaaaattttattttc
 cagacgctcaacttaacaccaacagcaagtgaatcgggagaacagcttatcccagtcaccgccaagatctcatagctaaaagcattaaagaagg
 atgtccgaagagaacttccaacgacttcatgtttcttcagagtatggcggaaggagcctacagccaggttggtgaacgaggaaatttcagaaat
 gtgtgcaactagtatcagagtacaaggaagcgttggaataactcggaatgcctgaattagtgcttgaagtaagcttgccatttttttcggaa
 catcggtgattctttcttggaattcaactgatagtactggtattacctagccgcaaaaatttcagtttttgcacaaatctatcttgacaca
 atatacctcactattagttaaatgctgagttttatcgattttttatagcttttttacttatgtatattcaaaatgtatgtgttttcaaatctt
 tttaaaggtttagtacggtcattaaaaaaatatttaaaatcatcttcagcgctaaaatgagcgactatcataagaaattagaaaatttggaa
 aaattgggtttattttttctagtccttgaaatttcaccttcccatttttatgctcactgtgtttcaaaactcatattccaacattgtaggaa
 ttctagaattgctttagatttctcttgttttccaatctttttactgtaagttatcatcattttggcaccgaaagggttttttaggtaatttta
 ccactgaccgtaacacttttccaatggcgtatacaatttgaaatttagcaacaaaaacaaaaaaacaaaaatcgtaccaagacggactactgtat
 tttttggcggaaaaatcgcccaattttgcgtcagggttacacgactgtgggaattgaaactcgactatgtaggccattcatgttgtctccccct
 gtccaatctcttttctccacaacactttaatctcatttcgcgtgagaagagaagaagaagatgcagaaaacgacgacatcgctcatagaattgt
 ctacacaaacctagtggtctgctctcttacacaaaataagccacgcgtctagcactatcaacattcgcaaacagctatacatgtgcttgttgaa
 gggaaaaacgagacgtttgtgtgtattggggagggttaattgaaccgtggtgtgtgggttcatcaaattgacagcgacagggatttgattttga
 acgtgttatcgcttggaccctgaggtatgtttctacacctagaacaaactaccgtaataatctttacattgacttttcggagagaagggtttgt
 actctgactatgtataactcaagaagaatgtagggaatttatgtcgttggaaacttccaatttggaaagtacagttttttggaaattaaattttga
 ttcttaaaatagtcgacttgaaataattttcgttatttatcaatccaatgagttgaaaaagtgaattgaaatttcttgactaaatccgtggaaa
 attatctagttttgttttccagataagttgtaaacactttgatagttaaataatgattgtttgtagtgtatcagaagcagaaaaatctgactagtttcc
 gccccccccctatacatatgatgcacacttaaaatgtccaagtgtgtttgaatagcaaatcttgaaaaacgtaaaaaacaataatttttcta
 tatctgtaaatattttcaacgaattttcagcttccaaattttggtcgtttttggatctttttacaaaaaaatattttatcaactgacactgata
 atattttctgcctcatattaaaaaatattcctctagcaaaaactgtaagttgaacgaatttacaataaaaaacacagctgcactgacaaaaaac
 aattacactggccaaaattgagcttgactgaccgagtttagcgaccatattctttttgtctaatttgggtgtgtgcggcggaatttcggcaaaat
 tgcgcagctcggaacacagaaaatttggcaaatcccgcaaaccttcaactgaagccactattgcacattaactgtcaaaattctggatataa
 ttagcaaaaacaataagtaaacatttctgaaaaattagaacctttcccgcatgtattttagtagcgcacctaaaaaatttcaaaacacaaaaaaca
 agcttccagtaaaaccctaataattccaggtattccgatgtcggaagtggcaacagatgcgatgttcgccgtcaaagtgtccagaagtcgtacc
 tcaaccgccatcaaaaaatggacgcaatcattcgcgagaagaatatcttaacatacctgtcacagaatgcgggtggtcatccgtttgtcacacag
 ctctacacacattttcacgaccaggctagaatttgtgagtttttccagcgccaaggttctttctgaaccatcaaaatccacttgtgatcatt
 ttattccaataaaaacgtcaacttaaaaaaaattaaacctcaattaatattcagatttctgtgatcggtgttgaaaatgggtgatcttggcg
 agtcgctgtgccattttggatcattcgacatgctcacctcaaaattctttgcctcggaatcttcacggactgcaattcctacacgacaacaaa
 attgtgcacagagacatgaagccggacaatgtgctcatccagaagacgggtcacattctcatcacagattttggaagtcccaggcggtttggcg
 tctccaactgtcacaggagggtttacggatgcgaatcaggcaagctcgcatcttcggattctggatcgccgcgcgcaactcgattctattcgg
 atgaggagggttaagggttttcggaatttactgaacaatttttgcagttccagaagagaacactgctcgacgtaccacatttgttggaaactgc
 tctctacgtgagcccgagatgctagctgacggagatgtgggaccacagtaagctccgattctttgtagaatgtcaaatttaacagttggatttc
 agaaccgacatttggggattgggatgtatcctttccagtgcttagccggacagccaccattcagagccgtcaaccagtagcatctttgaaaag
 aatccaggagttggatttctcgttccagaaggatttccagaggaagcgtcggaattatcgcaag

Fig. 35A

attttgtaggttgacatgaaacttttaaaactgaatacgttaattttcaacttacaggtgcgagaccgagtagccgtagcaccagtcaagaact
 tatggctcacaagttttttgaaaacgttgactgggtgaacattgcaaatatcaagccaccagtcctgcaagcctacattccagccacatttggcg
 agccggagtagtactacttaacattgggcctgtcgagccgggacttgatgatcGTGCCCTTGTTCCGTTTGATGAATTTGGGAAATGATGCTAGCGCA
 TCACAGCCATCAACGTGAGTTTGAAGCATTTTTTCTTGCAATTAAGTTTACCTTGCACTGACCAAAATTTATTGAAACTATTAATTATTGA
 TTCTGATTAACAATGACCAAAAGATTGAACTGACAAAGTGCAAAATTTGCACCGACCAAAAACAGTTTGCACTGACCACCTCTTCATTGCACT
 GACCACCTCTTCATTGCACTGACCAACTTTTCATTGCACTGACCATCTCTTCATTGCACTGACCAACTTTTCATTGCAATTCGGCAATGA
 TTCTTTGCACTCTACTGATCAAAAATGATTCAATCAATTAATTTCTTTGACAGTACTATGCCCTTATTCAAGGAGATGCTGATCTGAAAATTC
 TCAATAGTTGATAAAAATTACTAACCCCTTAGAAAGTTTCAGACCGCTTAACGTGGAACATCGCGGAGACCCATTTGTTTCGGAAATTCACCGT
 GAGTGATTTGCACCTAATTGGTTATTTTAAATAATCAATTAATTTATAGACGCGCCAATTCGGAAGCCGAAAAGAACCGCGCCGACGTGCCGAGA
 AGCTCGAAGAGCAACGTGTCAAAAACCCATTCCACATCTTCACCAACAACCTCGCTCATTTTGAAACAAGGATATTTGGAAGAACCGGAGGATTG
 TTTGCCAGACGCCGAATGTTCTGTGACCGAAGGACCGCATCTCTGTACATTGATGTGCCGAATCTTGTGCTCAAAGGAGAGGTACCATGGAC
 GCGGTGCATGCAGGTGGAGCTAAAAAATCGGGAACCTTCTTTATACATACGGTACGTGAGAAATAATCATAGCTGTCTATCTCATTATAGTACTC
 AATGAATCTGAAAATTTCAAATTTTCAGCCCAACCGCTCTACTACTTGTGATCTCGAAAAGAAGCAGATGAGTGGTGAAGCCTATCAATG
 ATGTTCCAGCGGTACTCGGTGACTATCGAAAAGACTTTTAACTCTGGGATGCGTGACGGAACATTTGGCAGCATTTATGGAAGCAAAAGTCC
 AGAAAGSTATGAATTACTGGAAGGCCCCCTCACTGAGTTTCCAGCAAGTTTCAGAGTTTTTTATTGGAATTTTGGCAATTTTCATTAGACTTTA
 GAGCCTATTGCTATTTTGTGGACAGGTTTAAACATTTTCAAAAAAATTTGAGAAATGTCTCAAAAAATTTGGAGTGTGACAGTTTTCTGAATTT
 TGAAAATCTGTTCTCAAAATTGATTTTACAGAGCTTGTTCGAGATTTTCATAATCCTTCAAAAGATATAGAATATTTGTGTTCAACTTTTC
 TTGTCAAAATATTTTTTTTGGACAATCTAGATTCTGGAAAATTTTCAAAAAAAGATAATCTCTAAACAAAACATAATTTCAAATGTTCTAAAGGT
 TCTTTATTTTCCATGCAACTCTAAAATCTTCCCGTATATTTTTTGGAAAGTCTTATGATGTTTAGACGGTTTAAATTTTTTGTGATTTAAAT
 TTTTAGGGTGGTCTATAATTTTGGACCACCCTGTATAATTATGGACCACCATGTACACTTATAGACCACCCAGTAACAAGCATTTTGGACCAC
 CACGCAATCTTATTATTATGGACCACCAAACTTAGAACACCTTCAATACTTCTTTCTGTTCAAAAAATGATCAACTTGCTGAAAAAATTT
 TTTGTAGGAAATGATGCGTGAACAGAGCGCTGCGCCGCAACAAGAAAAGGAGAGAAAAAGGCCCTAAAAGCCGAGCAAGTGACCAAGAAGC
 TTCAATGCAATGGACAAGAAGTCGCTTGAAGGCTCACCTCCCTTCTACTCCCCACAAAATCACCATCAACCAATCACACTTTTGTATCATT
 TTGCGTCC

Fig. 35B

MEDLTPTNTSLDTTTTNNDTTS DREAAPTTLNLTPTASESENSLSPVTAEDLIAKSIKEGCPKRTSNDFMFLQSMGEG
 AYSQVFRCREVATDAMFAVKVLQKSYLNRHQMDAIIREKNILTYLSQECGGHPFVTQLYTHFHDQARIYFVIGLV
 ENGDLGESLCHFGSFDMLTSKFFASEILTGLQFLHDNKIVHRDMKPDNVLIQKDGHILITDFGSAQAFGGLQLSQEGFT
 DANQASSRSSDSGSPPTRFYSDEEEENTARRTTFVG TALYVSP EMLADGDVGPQTDIWGLGCILFQCLAGQPPFRAV
 NQYHLLKRIQELDFSFPPEGFPPEEASEIIAKILVRDPSTRITSQELMAHKFFENV DWNIANIKPPVLHAYIPATFGEF
 EYYSNIGPVEPGLDDRALFRLMNLGNDASASQPSTPSNVEHRGDPFVSEIAPRANSEAEKNRAARAQKLEEQRVK
 NPFHIFTNNSLILKQGYLEKKRGLFARRRMFLLTEGPHLLYIDVPNLVLKGEVPWTPCMQVELKNSGTFFIHTPNR
 VYYLFDLEKKADEWCKAINDVRKRYSVTIEKTFNSAMRDGTFGSIYGKKKSRKEMMREQKALRRKQEKEEKAL
 KAEQVSKKLSMQMDKKSP

Fig. 36

MEDLTPTNTSLDTTTTNNDTTS DREAAPTTLNLTPTASESENSLSPVTAEDLIAKSIKEGCPKRTSNDFMFLQSMGEG
 AYSQVFRCREVATDAMFAVKVLQKSYLNRHQMDAIIREKNILTYLSQECGGHPFVTQLYTHFHDQARIYFVIGLV
 ENGDLGESLCHFGSFDMLTSKFFASEILTGLQFLHDNKIVHRDMKPDNVLIQKDGHILITDFGSAQAFGGLQLSQEGFT
 DANQASSRSSDSGSPPTRFYSDEEVPEENTARRTTFVG TALYVSP EMLADGDVGPQTDIWGLGCILFQCLAGQPPFR
 AVNQYHLLKRIQELDFSFPPEGFPPEEASEIIAKILVRDPSTRITSQELMAHKFFENV DWNIANIKPPVLHAYIPATF
 GEPEYYSNIGPVEPGLDDRALFRLMNLGNDASASQPSTFRPSNVEHRGDPFVSEIAPRANSEAEKNRAARAQKLEE
 QRVKNPFHIFTNNSLILKQGYLEKKRGLFARRRMFLLTEGPHLLYIDVPNLVLKGEVPWTPCMQVELKNSGTFFIH
 TPNRVYYLFDLEKKADEWCKAINDVRKRYSVTIEKTFNSAMRDGTFGSIYGKKKSRKEMMREQKALRRKQEKEE
 KKALKAEQVSKKLSMQMDKKSP

Fig. 37

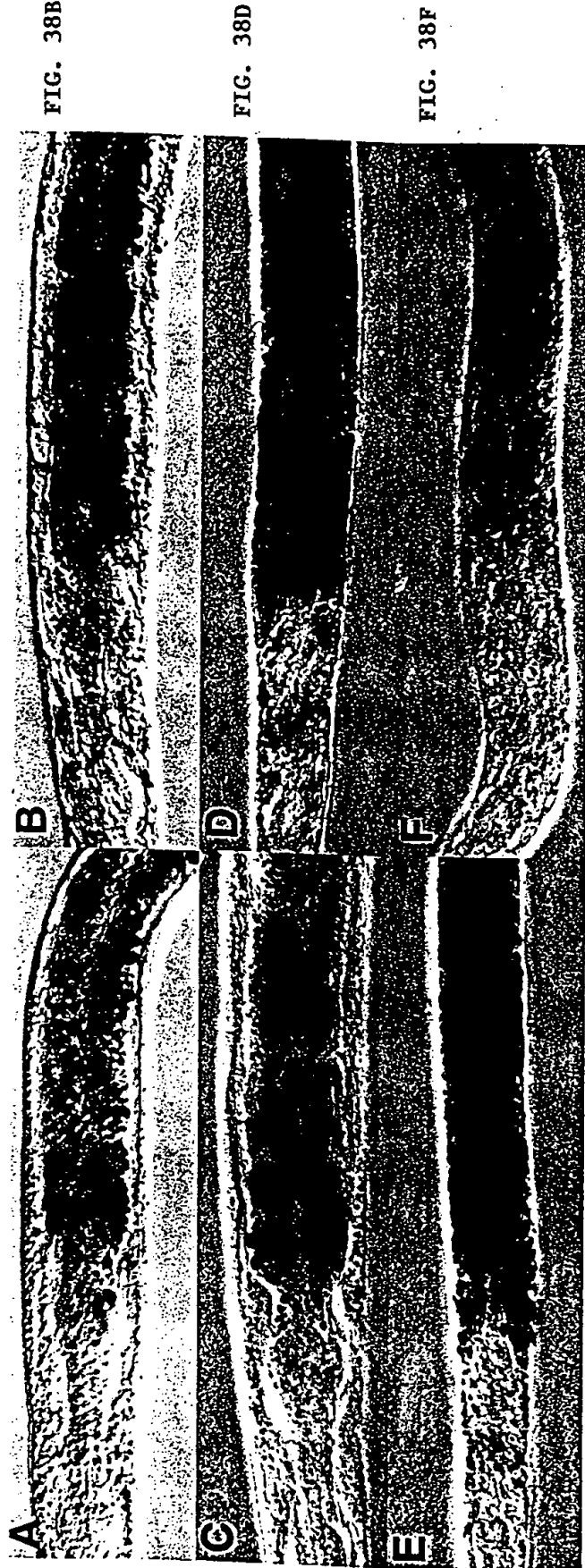


FIG. 38B

FIG. 38D

FIG. 38F

FIG. 38A

FIG. 38C

FIG. 38E

PO BOX 670



Q A L T Q M N P K
caagcgttgactcaa atgaatccaaaa

Q A L T Q C V D S M R *

DAF-18	48	IFRTAVSSNR	CRTEYQNIDL	DCAYITDRLL	ALGYPATGIE	ANFRNSKVQT
PTEN	4	ILKEIVSRNK	RRYQEDGEDL	DLTYIYPNLI	AMCFPAERIE	GVYRNINDDV
DAF-18	98	QOELTRRHCK	GNVKVENIRG	GYVDADNFD	GNVICFDMUD	HEPPSLELMA
PTEN	54	VRELDSKH.K	NHYKIYNLCA	ERHYDTAKFN	CRVAQYPFED	HNPEOLELIK
DAF-18	148	PECREAKEWL	EADDKHVTAV	HCKAGKGRTG	WVICALLIYI	NEYPSPRQIL
PTEN	103	PECEDLDQWL	SEDDNHVAAL	HCKAGKGRTG	WVICALLLHR	GKFLKAQEA
DAF-18	198	DVYSIIRTKN	NKGVTTIPSQR	RYIYVYHKLR	ERELNYLPLR	MQLIGVYVER
PTEN	153	DIFYGEVTRD	KKGVTTIPSQR	RYVYVYSYLL	KNHLDYREVA	LLFHKTMFET
DAF-18	248	PKTWCCGSK	IKVEVNGNST	ILFKPD..PL	IISKSNHQRE	RATWNNCDT
PTEN	203	IFMFGGTCN	PQFVVCQLKV	KIYSSNSGPT	RREDKFMYYE	FPQFLPVCGD

FIG. 39B

0963697.092504
105250.2692960

DAF-18 Protein

MVTPPPDVPSTSTRSMARDLQENPNRQPGEPVSEPYHNSIVERIRHIFRTAVSSNRCRTEYQNIDLDCAYITDRIIAIG
YPATGIEANFRNSKVQTQQFLTRRHGKGNVKVFNLRGGYYYDADNFDGNVICFDMTDHHPSPSLELMAFPFCREAKEWLEAD
DKHVIAVHCKAGKGR TGVMICALLIYINFYPSPRQILDYYSIIRTKNNKGV TIPSQRRYIYYYHKL RERELNYLPLRMQL
IGVYVERPPKTWGGGSKI KVEVGNGSTILFKPDPLIISKSNHQ RERATWLN NCDTPNEFDTGEQKYHG FVSKRAYCFMVP
EDAPVFVEGDVRIDIREIGFLKKFSDGKIGHVWFNTMFACDGG LNGGHFEYVDKTQPYIGDDTSIGRKNGMRRNETPMRK
IDPETGNEFESPWQIVNPPGLEKHI TEEQAMENYTNYGMI PPRYTISKILHEKHEKGIVKDDYND RKLPMGDKSYTESGK
SGDIRGVGGPF EIPYKAEHVLTFPVYEMDRALKSKDLNNGMKLHVVLRCVDTRDSKMM EKSEVFGNLAFHNESTRRLQA
LTQMNPKWRPEPCAFGSKGAEMHYPPSVRYSSNDGKYNGACSEN LVSDFFEHRNIAVLNRYCRYFYKQRSTSR SRYPRKF
RYCPLIKKHFIYPADTDDVDENGQPF FHSPEHYIKEQEKIDAEKAAKGI ENTGPSTSGSSAPGTI KKTEASQSDKV KPAT
EDELPPARLPDNVRRFPVVGVD FENPEEESCEHKTVESIAGFE PLEHLFHESYHPNTAGNMLRQDYHTDSEVKIAEQEAK
AFVDQLLNGQGV LQEFMKQFKVPSDNSFADYVTGQAEVFKAQI ALLEQSEDFQRVQANAEEVDLEHTLGEAFERFGHVVE
ESNGSSKNPKALKTREQMVKETGKDTQKTRNHVLLHLEANHRVQIERRETCP ELHPEDKI PRIAHFSSENSFSDSNFDQAI
YL

FIG. 40A


```

1  ttccagggtac atctactaac ccccaatggt tactcctcct ccagatgtgc caagcacatc
61  gaccagggtcg atggctcgtg accttcaaga gaatccaaac cgacaacctg gtgaaccacg
121 tgtgtctgaa ccgtatcaca attcaatcgt cgagcggatt cgccatattt ttcggacggc
181 tgtatcttcc aatcggtgtc gcaccgagta ccaaaatata gacctagatt gtgcataat
241 cacagaccga atcatagcta tcggttatcc agcaacagga atcgaagcga atttccgtaa
301 ctcaaaagtt caaactcaac aatttctgac caggcggcac ggaaagggca acgtgaagggt
361 gtttaacctg cgcggtggat actactacga tgcggataac ttcgatggaa atgttatttg
421 cttcgatatg actgatcatc atccgcgag tctcgaatta atggctccgt tttgcagaga
481 ggctaaggaa tggcttgaag cagacgataa acatgtaata gctgtacact gtaaagctgg
541 aaaaggccgt accggagtga tgatatgtgc tcttctcatc tacatcaact tctatccgag
601 cccacgacaa attctcgact actactcaat aattcgtaca aaaaacaaca aagggtgtcac
661 aattccatca caacgacgct acatttacta ctaccataag cttcgtgaac gtgagctcaa
721 ctatttacca ttgagaatgc agttgattgg tgtctacgtg gaacggcctc caaagacatg
781 ggggtggtggt tcaaagataa aagtggagggt tggaaatggc tcgacaattt tatttaagcc
841 ggatcctctc ataatctcca aatcaaatca tcagcgagag cgtgcgacgt ggctgaacaa
901 ctgtgatacg cctaacgaat tcgacaccgg agagcaaaaa tatcatggat ttgtttccaa
961 gagagcatac tgttttatgg tgccagaaga tgctccagta tttgtcgaag gagatgttcg
1021 tatagacatt cgcgaaatcg gatttctcaa aaagttttcg gacgggaaga ttgggtcatgt
1081 ttggttcaat acaatgttcg catgtgatgg aggactcaac ggtggacatt tcgagtacgt
1141 agacaaaact cagccgtaca tcggagacga tacatcaatc ggacggaaaa atggaatgcg
1201 aagaaatgaa acgccgatgc gaaaaattga tccagaaact ggaaatgaat ttgagtctcc
1261 gtggcacaata gtgaatcctc ctggactgga aaaacatatt acggaggaac aagcaatgga
1321 aaattatacc aattatggca tgattcctcc tcgatacacg atcagcaaga ttcttcacga
1381 aaagcatgaa aaaggatatc tcaaggatga ctataatgat cgtaagctgc caatgggaga
1441 caaatcatac acggaatcag gaaaaagtgg agatattcga ggagtcggtg gtccatttga
1501 gataccatat aaagctgagg aacatgttct cacatttcca gtttatgaaa tggatcgagc
1561 attgaagagt aaagatctta acaacggaat gaaacttcac gttgttcttc gttgtgtaga
1621 tactcgtgat tcaaaaatga tggaaaagag cgaagtgttc ggcaatctgg cattccataa
1681 tgaatcgaca cggaggcttc aagcgttgac tcaaatgaat ccaaaatggc gacctgaacc
1741 gtgtgctggt ggatccaaag gtgctgaaat gcattaccct ccgtcgggtc gatattcaag
1801 caatgatgga aagtataatg gagcctgcag tgagaacctt gttagcgatt ttttcgagca
1861 cagaaatatt gccgttctta atcgatattg ccgatatctc tacaagcaac gcagtacatc
1921 tcgaagccgt tatccaagaa aattcagata ctgtcctctg atcaagaaac atttctacat
1981 tccagctgat accgatgatg ttgatgaaaa tgggcaaccg ttcttccact caccagagca
2041 ttacattaaa gaacaggaaa aaatagacgc agagaaagca gctaaaggaa ttgaaaatac
2101 tggaccaggt acttcaggat caagtgtctc cggaactatc aagaaaacgg aagcttcaca
2161 atccgacaag gtgaagccgg caactgaaga cgaacttctc cctgcgaggc taccggataa
2221 tgtgcgaaga tttccagtcg tcggcggtga tttcgaaaat ccggaagaag aatcgtgtga
2281 acacaaaacc gttagagtcaa tagctgggtt tgaaccactc gaacatctat tccatgaatc
2341 ataccatcca aatacggccg gtaacatgct gcgtcaggat tatcacactg attcgggaag
2401 gaaaatagct gaacaagagg caaaagcctt cgttgaccag ttgcttaatg gacaaggtgt
2461 attacaagag tttatgaagc aattcaaagt accatcggac aattcctttg ctgattatgt
2521 aaccggacag gccgaagttt ttaaagcaca gattgcgtta ctggagcagt cggaggattt
2581 tcaacgagtt caagcgaatg cagaggaagt cgatcttgaa cacactcttg gtgaagcgtt
2641 tgagcgattc gggcacgttg tagaagaatc gaatggttct tctaaaaatc caaaagccct
2701 gaaaactcga gaacaaatgg tgaaagaaac tggcaaagac actcagaaga cccgcaatca
2761 tgtgcttcta catttgaag ctaatcatcg tgtgcaaatc gagcgtcgtg aaacgtgccc

```

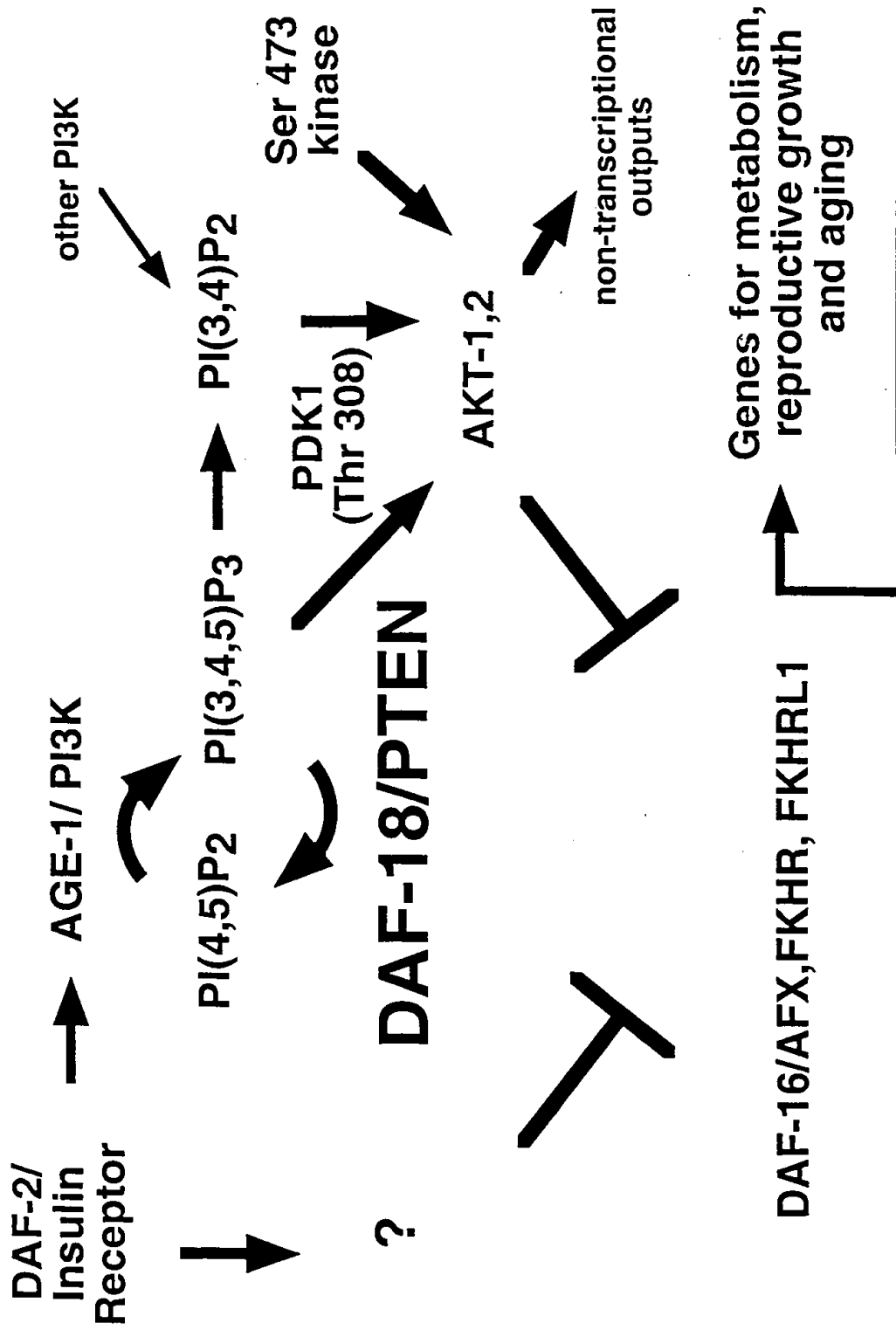
FIG. 40B

2821 ggagctacat ccagaggata aaatcccaag aattgctcat tttccgaaa acagcttctc
2881 ggattcgaat ttgatcaag ctatttattt gtaaacctaa aacaaaactt ttagaagatt
2941 ttcttcttac tgacctcca attttcagat aatttcaatg ttttaagttt tctcttcaaa
3001 gtatcattca ctttctgtat agtgttttgt tttttaacaa actattgttc gattattttg
3061 tatattcata ttatagctct caacttcccg attttccacg tatatatgta tattttgccg
3121 ggtgaaaaat agcaattccc tatgaatgta tccccctcca tctgttttct tactcagaaa
3181 ttgtaattca cattgcgggt catcactaat cctatgggct ttaacacaat tctcccataa
3241 attaatgta cttaccaatt ttttgtttaa ttatttagat ttgtaacatt gaaattggtg
3301 ataa

FIG. 40B

0996369-099504

FIG. 41



ttta

attacccaagtttgaggtagcattgctctcttcaatcat atg gat tcg ttg ttt cag atg gca tcc gca
M D S L F Q M A S A

atg aag ttt caa tac tac tcg aag aaa gct gct gga aag aca atg tct aat agt gtc tcc
M K F Q Y Y S K K A A G K T M S N S V S

atg tcc agt gac aat cgc atg gag gat ttt aaa cgt cgt ttt cgt cga agt gga tcg tta
M S S D N R M E D F K R R F R R S G S L

gga att cca ttt gtc cca gaa gaa gat gtt aaa caa ctc ttc aca cca act cgt act gtt
G I P F V P E E D V K Q L F T P T R T V

cgt cga gaa gca tct att cgc gaa ggg gat gag gaa gaa gga gta caa att ctc aca ata
R R E A S I R E G D E E E G V Q I L T I

att gtc aag tca agt cgt gtt tcg gag gat atc tca aaa atg att gca aac ctc cct gat
I V K S S R V S E D I S K M I A N L P D

cac act cgt atc aaa cat ttg gag act cgt gac agt caa gat gga agt tcc aaa act atg
H T R I K H L E T R D S Q D G S S K T M

gat gtt ctt cta gag att gag ctc ttt cat tat gga aaa caa gaa gca atg gat ctt atg
D V L L E I E L F H Y G K Q E A M D L M

aga ctt aat ggg ctt gat gtt cat gag gtg tca tcg act att cgt cca act gca ata aaa
R L N G L D V H E V S S T I R P T A I K

gag caa tat aca gag cct gga tct gat gat gcg aca acc ggt tct gaa tgg ttt cca aaa
E Q Y T E P G S D D A T T G S E W F P K

agt att tat gat ttg gat att tgt gca aaa aga gtg att atg tat gga gca ggg ctg gac
S I Y D L D I C A K R V I M Y G A G L D

gct gat cat cct ggt ttc aaa gat acc gag tat cgt caa cgt cga atg atg ttt gct gaa
A D H P G F K D T E Y R Q R R M M F A E

ctg gcg ctc aat tac aaa cac ggt gag cca att ccg cga acc gaa tat aca tca tcc gaa
L A L N Y K H G E P I P R T E Y T S S E

cgg aaa act tgg gga att ata tat aga aaa ttg aga gaa ttg cac aaa aag cac gca tgc
R K T W G I I Y R K L R E L H K K H A C

aag cag ttt ctt gat aac ttt gag cta ctg gag aga cat tgt gga tac tcg gaa aat aat
K Q F L D N F E L L E R H C G Y S E N N

att ccg caa cta gaa gat atc tgc aag ttt ttg aaa gca aaa act gga ttc cgt gtt cgc
I P Q L E D I C K F L K A K T G F R V R

FIG. 42

cca gtc gcc gga tac tta tca gct cgt gat ttc ttg gca ggt ctt gca tat cgt gtc ttc
 P V A G Y L S A R D F L A G L A Y R V F

 ttc tgc act caa tac gtt cgc cat cat gcc gat cca ttt tac act cca gaa cca gac acc
 F C T Q Y V R H H A D P F Y T P E P D T

 gtt cac gag ctc atg ggt cac atg gct cta ttc gct gat cca gat ttt gct cag ttt tct
 V H E L M G H M A L F A D P D F A Q F S

 caa gag att gga tta gct tct ctt gga gca tca gag gaa gat ttg aag aag ctt gca aca
 Q E I G L A S L G A S E E D L K K L A T

 ctc tac ttc ttt tcc att gaa ttt ggt ctc tcg tct gat gac gct gcc gat tct cca gta
 L Y F F S I E F G L S S D D A A D S P V

 aaa gaa aat gga tca aat cat gaa aga ttt aaa gta tac gga gca gga ctt ctg agc agt
 K E N G S N H E R F K V Y G A G L L S S

 gct ggc gag ttg caa cat gcc gtt gag ggt agt gca acc att att cgt ttt gat ccg gat
 A G E L Q H A V E G S A T I I R F D P D

 cgt gtt gtt gag caa gaa tgt ctc att act act ttc cag tca gcg tat ttc tat act aga
 R V V E Q E C L I T T F Q S A Y F Y T R

 aat ttt gaa gag gcc cag cag aaa ctc aga atg ttc acc aac aac atg aaa cgt ccc ttc
 N F E E A Q Q K L R M F T N N M K R P F

 att gtt cgt tac aac cca tac aca gaa agc gtc gaa gtt ctc aac aac tcc cgt tcc att
 I V R Y N P Y T E S V E V L N N S R S I

 atg ttg gca gtg aac tct ctc cgc tca gac atc aac ctg ctc gcc gga gct ctc cac tac
 M L A V N S L R S D I N L L A G A L H Y

 atc ctg tag
 I L *

FIG. 42

09369-09369

FIG. 44A

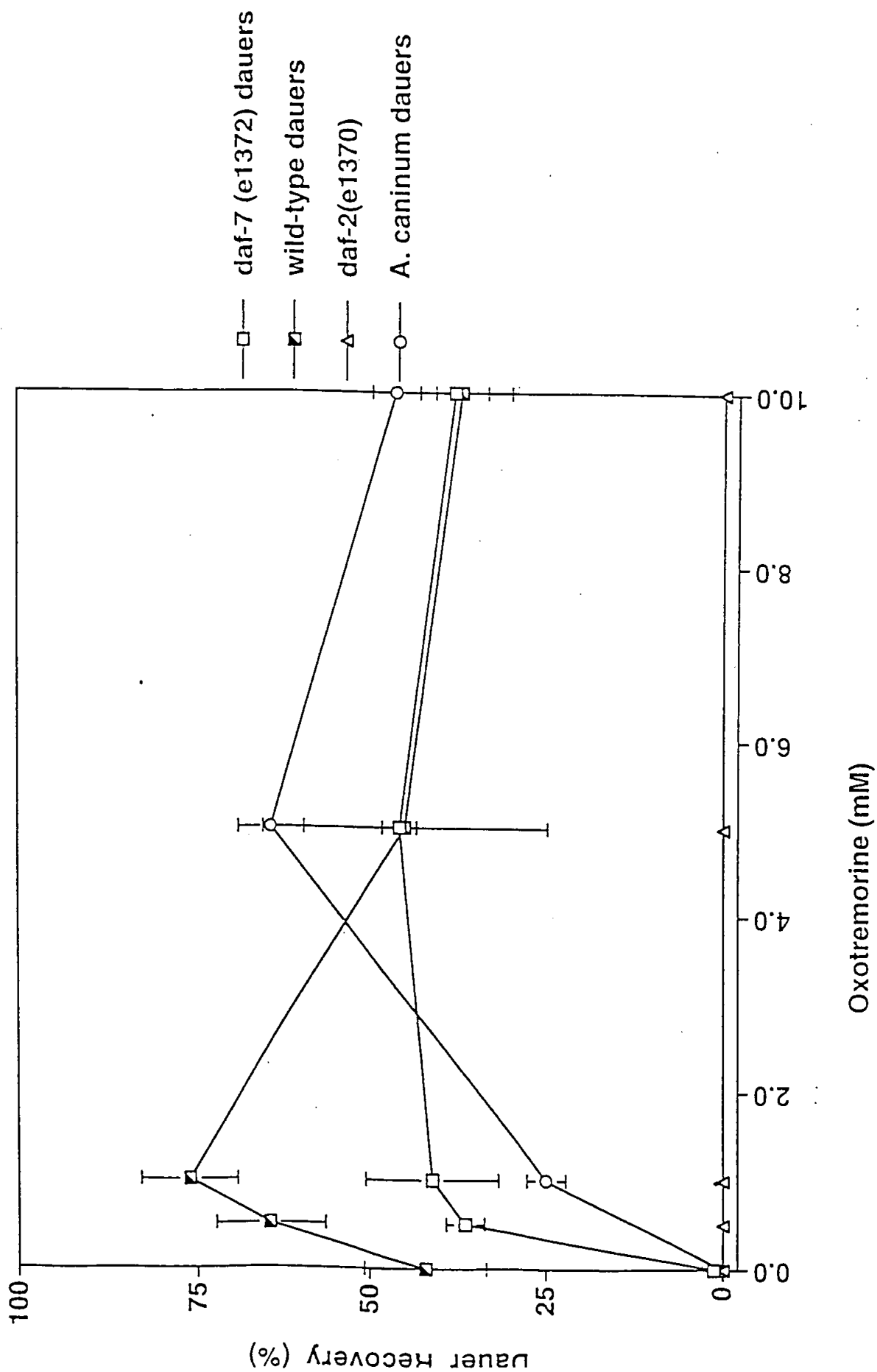


FIG. 44B

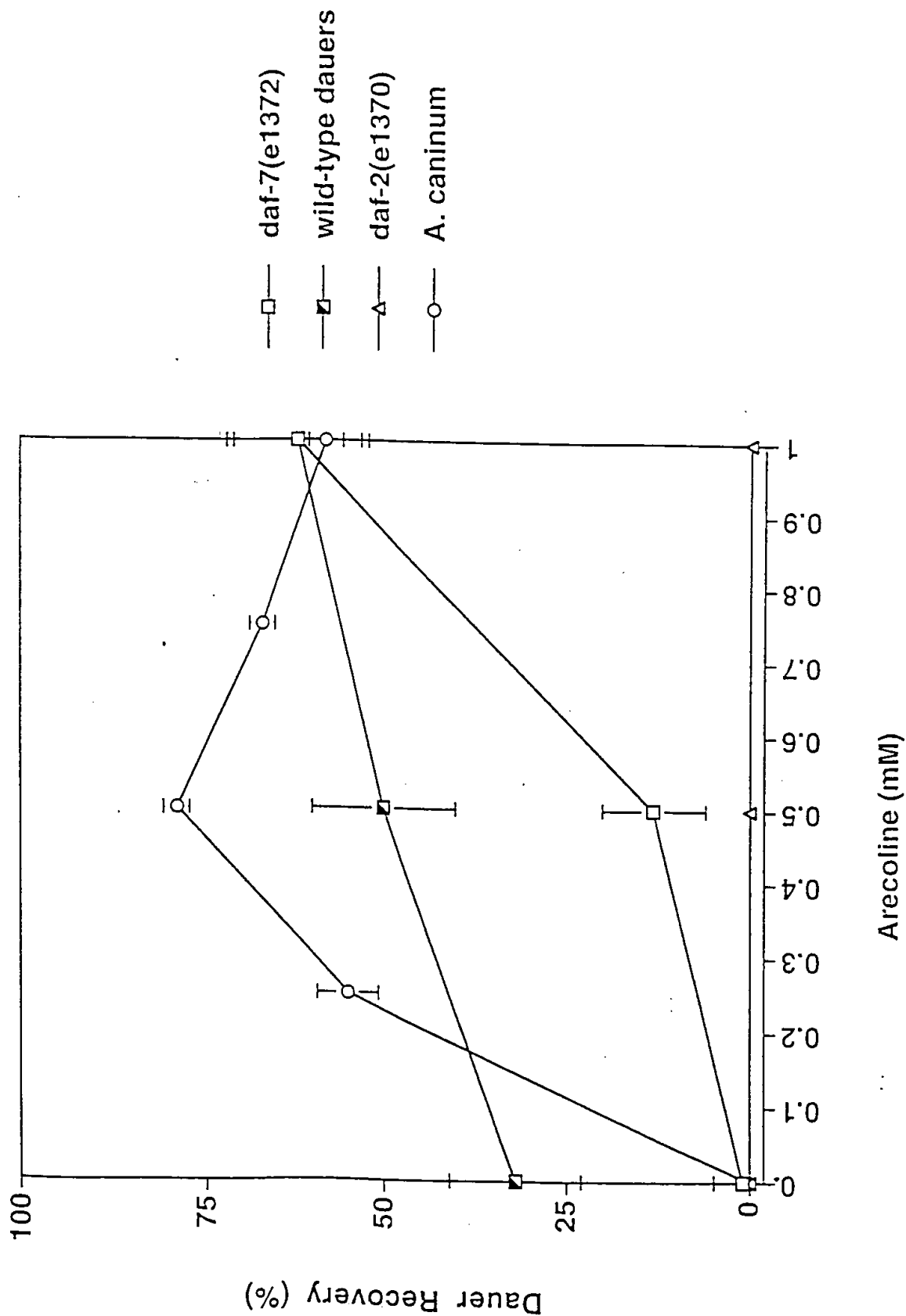


FIG. 45A

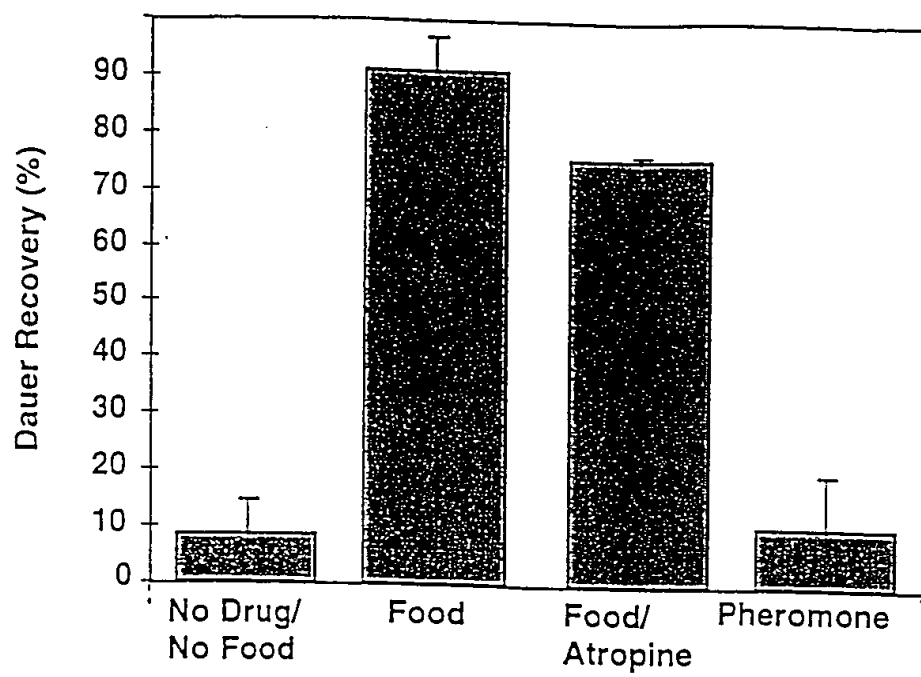


FIG. 45B

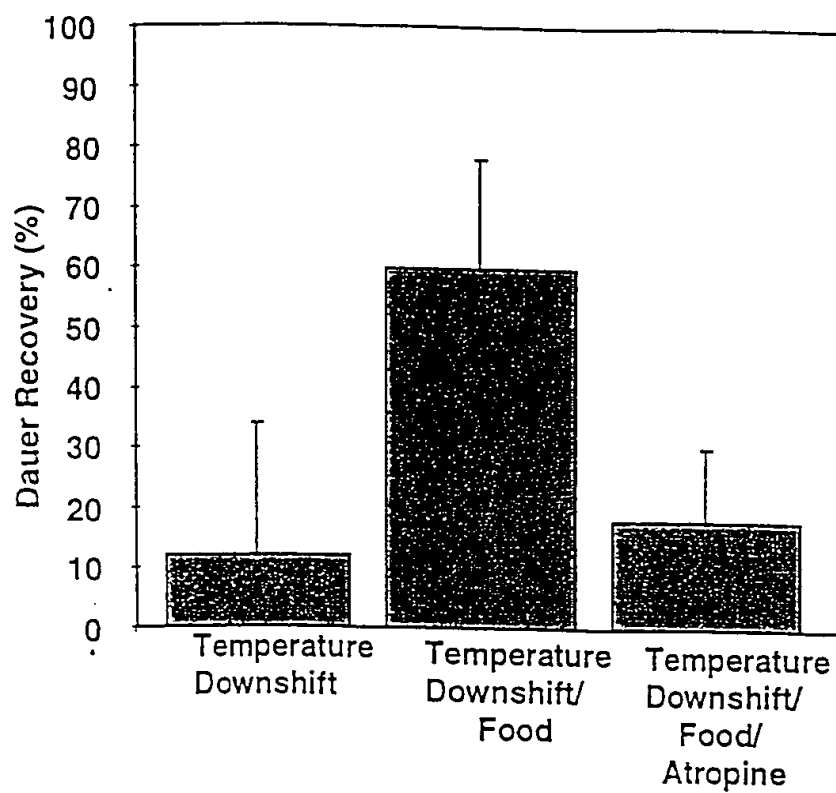
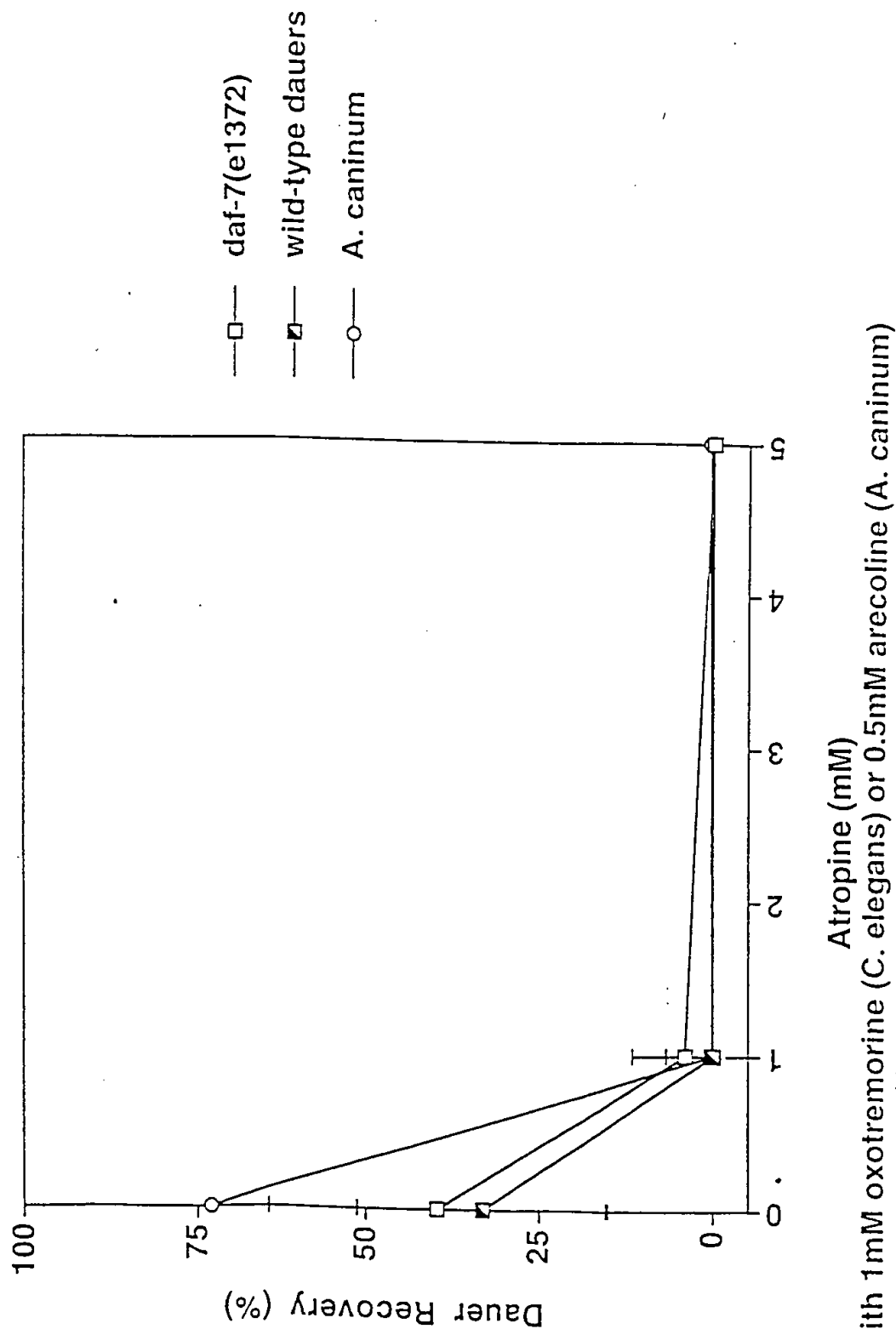
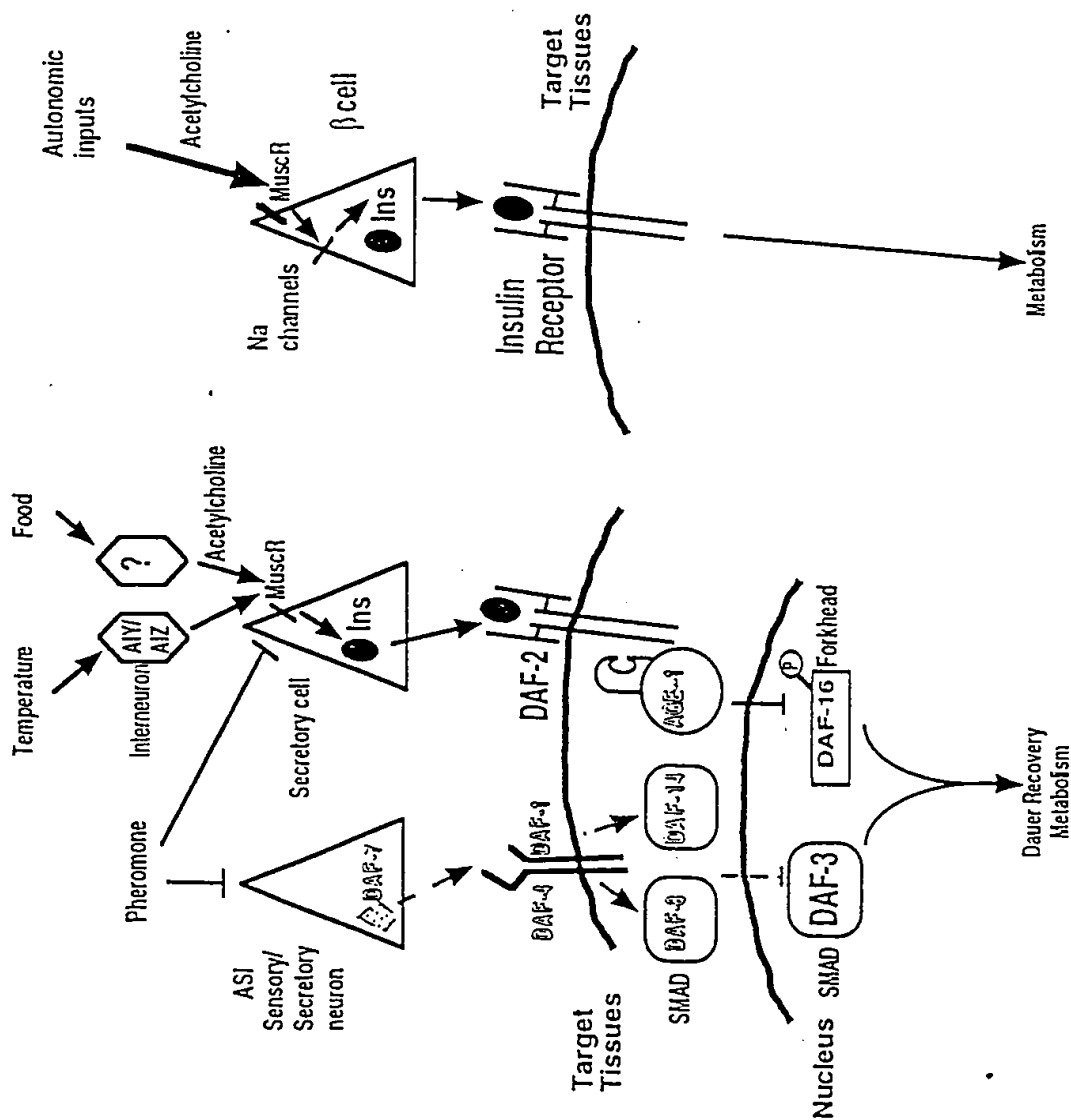


FIG. 44C



C. elegans

Mammals



ATTCGGCATGAGCATGGaGCTTCGAGTCCTAGAGAACACAAAACGTTCCCGGCGGAACCTGGGtCTGGACTGCGAC
GAGACTCAAGCGAGTCCCGCTGCTGCCGATATCCCCTCACAGTGGACTTTGAGGCTTTCGGCTGGGACTGGATCAT
CGCACCTAAGCGCTACAAGGCCAACTACTGCTCCGGCCAGTGGGAGTACATGTTTCATGCAAAAATATCCGCATACC
CATTTGGTGCAGCAGGCCAATCCAAGAGGTTATGcTGGGCCCTGTTGTACCCCCACCAAGATGTCCCAATcAACA
TgcTctACTTCAATGACAAGCAGCAGATTATcTACGGCAAGATCCCTGGCATGGTGGTGGATCGCTGTGGcTGCTC
TTAAGGTGGGGGATAGAGGATGCCTCCCCACAGACCGTACCCAAGACCCATAGCCcTGCCCAATCCACCGCCTG
ATCCAAACAT

FIG. 47A

IRHEHGASSPREHKTFPAEPGSLRRDSSSESRCRYPLTVDFEAFGWDWIIAPKRYKANYCSGQWEYMFQKYPHT
HLVQQANPRGYAGPCCTPTKMSPINMLYFNDKQQIIYGKIPLAMVVDRCGCS

FIG. 47B

09963693-092501